APPENDICES TO THE

REPORT TO THE *AD EOC* ADVISORY COMMITTEE

OF THE

HARVARD UNIVERSITY

TOBACCO AND HEALTH RESEARCH PROGRAM

1003535593

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

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APPENDIX I

A. TOBACCO INDUSTRY POLICY STATEMENT ON RESEARCH ON SMOKING AND HEALTH.

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Tobacco Industry

Research on Smoking and Health

For the past two decades, hundreds of scientists have performed thousands of experiments and written millions of words in a dedicated effort to explore the question of smoking and health.

Result: So far, in spite of this massive effort, there are eminent scientists who question whether any causal relationship has been proved between cigarette smoking and human disease--including lung cancer, coronary heart disease, or emphysema. They believe that years more of exhaustive investigation will be required to clear up what is indeed now a muddy picture.

What has been learned is this: Establishing cause-and-effect relationships, which have been claimed to exist by government agencies and other groups, is much more complex than originally thought. In fact, even those who claim a cause-and-effect relationship has been proved admit that no particular ingredient, as it occurs in cigarette smoke, has been demonstrated as the cause of any particular disease.

Who sponsored the research

There are those who believe that voluntary health associations have provided the money for most of this research. Others think it was strictly a project of the various U.S. Government departments.

It is true that both have been--and continue to be--active in this field. But, a major portion of this scientific inquiry has been financed by the people who know the most about cigarettes and have a great desire to learn the truth...the tobacco industry.

And the industry has committed itself to this task in the most objective and scientific way possible.

A $65,000,000 program

In the interest of absolute objectivity, the tobacco industry has supported totally independent research efforts with completely non-restrictive funding.

In 1954, the industry established what is now known as CTR, the Council for Tobacco Research-USA, Inc., to provide financial support for research by independent scientists into all phases of

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tobacco use and health. Completely autonomous, CTR's research activity is directed by a board of 11 scientists and physicians who retain their affiliations with their respective universities and institutions. This board has full authority and responsibility for policy, development and direction of the research effort. Each researcher receiving a grant has complete freedom to publish the results of his work, whatever the results may be. As of June of this year, CTR has made grants totalling more than 44 million dollars.

In 1964, the tobacco industry made a commitment for additional independent research that amounted, during a ten-year program, to 15 million dollars. This commitment was made to AMA-ERF, the Education and Research Foundation, an arm of the American Medical Association. Under this program the ERF, like the CTR, made grants for scientific research with complete freedom and autonomy.

What they did

As of January 1977, the Council for Tobacco Research alone has awarded grants to 371 scientists, with numerous renewals, in 247 medical schools, hospitals and research institutions in this country and 10 other countries.

During the ten years of the Education and Research Foundation program 222 grants were awarded to scientists in 87 medical and research institutions.

While the projects of these researchers may be considered relatively narrow in individual scope, the industry has not overlooked its research responsibilities in broader areas. In 1970, Washington University in St. Louis announced two million dollars in tobacco industry funding for study of immunologic factors in cancer. The grant has since been increased to 2.8 million dollars. In 1972, Harvard Medical School announced receipt of a 2.8 million dollar tobacco industry grant for a five-year investigation into pulmonary and cardiovascular diseases. The research program was extended for another three years with an additional $2.2 million grant announced by the University in March 1977. And in 1974 the UCLA School of Medicine announced a 1.7-million-dollar, industry-financed, five-year program of research on lung defense mechanisms and early detection and treatment of cancer.

The combined commitment by the tobacco industry for all these projects amounts to more than 65 million dollars. In many years, the tobacco industry's commitment in this area has exceeded that of any government department...and has come to millions more than the research expenditure on smoking and health reported by all the voluntary health associations combined.

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What they found

The findings of research studies funded in whole or in part by the industry have already resulted in publication of more than 2,000 scientific papers in the professional literature.

Through this work much valuable data have been produced about lung cancer, heart disease, chronic respiratory ailments and other diseases. However, there's still a lot more to be learned.

The findings are not secret

All the above reports have been published in medical and scientific journals in the United States and other parts of the world.

These documents are available to scientists and doctors interested in pursuing the scientific truths on the smoking and health issue.

The work should go forward

There are eminent scientists who believe that the question of smoking and health is an open one and that research in this area must go forward.

From the beginning, the tobacco industry has believed that the American people deserve objective, scientific answers.

With this same credo in mind, the tobacco industry stands ready today to make new commitments for additional valid scientific research that offers to shed light on the question of smoking and health.

THE TOBACCO INSTITUTE
August 1977

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APPENDIX II

A. Harvard University - Tobacco Industry Agreement (1972-1977)

B. Harvard University - Tobacco Industry Renewal Agreement (1977-1980)

C. Supplemental Funding Award Guidelines

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SHOOK, HARDY, MITCHELL & BACON

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C. KEITH LARSON
JOHN C. MONICA
CHARLES R. WALL
HARVEY L. KAPLAN
SAM L. COLVILLE
DAVID M. ROBERTS

October 2, 1972

Gary L. Huber, M.D.
Chief, Division of Respiratory Disease
Harvard Medical Unit
City of Boston, Department
of Health and Hospitals
818 Harrison Avenue
Boston, Massachusetts 02118

Dear Gary:

In accordance with our telephone conversation of today, I am enclosing herewith a xerox copy of the signed agreement between Harvard Medical School and seven cigarette manufacturers. As I advised you, I will retain the original until we learn definitely whether there will be additional participants. It may be late in October before we will have a final answer to this question and until then there should be no publicity.

I understand that you will give consideration to the type of publicity which Harvard contemplates and will be in touch with me concerning that in the near future.

I am advised by Horace Kornegay that a partial payment by each of the committed participant companies is being forwarded to you today or tomorrow. The balance of the initial semi-annual payment will be forthcoming as soon as we hear from the other company.

Please advise if there are any questions. I know that the entire cigarette industry is pleased to have Harvard Medical School undertake this important research concerning smoking and health.

Sincerely,

David R. Hardy

David R. Hardy

DRH:sb
Enclosure

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HARVARD RESEARCH PROPOSAL

Harvard Medical School proposes to develop and implement a scientifically objective research program relative to smoking and health with the goal of providing major contributions toward the solution of some of the questions regarding cigarette smoking. A five-year research program to be supported by sponsoring tobacco companies is proposed on the following basis:

1. Direct responsibility for the development and administration of the program will be in the Harvard Medical School. Dr. Gary L. Huber will be the principal investigator. Drs. Franklin Epstein, Edward H. Kass and Ramzi S. Cotran will provide advisory assistance as project consultants. In the event Dr. Huber becomes unavailable prior to the completion of the research program, a substitute principal investigator with training, experience and integrity comparable to that of Dr. Huber will be selected by the Harvard Medical School. The sponsoring companies' continued support shall be contingent upon their approving any such substitute principal investigator.

2. The design and conduct of the research program will be exclusively the right and obligation of the principal investigator and all researchers will be free to publish results and data developed in the research program at such times and in such scientific journals as they may elect, subject to the prior approval of the principal investigator.

3. There presently exists at Harvard Medical School under the direction of Gary L. Huber, principal investigator, a well-established program for the investigation of factors that may be important in the development of various diseases and host defenses to such diseases, including particularly host defenses to pulmonary diseases. The proposed program on tobacco research will generally proceed along the following four phases:

(a) Immediate utilization, redirection and implementation of existing resources of the already established program in order to study possible biologic effects of cigarette smoke upon the lung with the objective of determining the role, if any, that cigarette smoke may play in the development of pulmonary disease.

(b) Rapid expansion of existing resources to include a

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more comprehensive endeavor in the areas of (i) biochemistry, (ii) pathology and (iii) epidemiology, relative to questions of health and cigarette smoking.

(c) Development of limited resources for the study of potential relationships between cigarette smoke and cancer of the lung.

(d) Development of efforts, independently or in collaboration with other private research facilities, to study possible relationships between cigarette smoke and heart and vascular diseases.

4. The budget for the program is set forth in Appendix A, attached. It is presently anticipated that payments will be received in equal semiannual installments over the five-year period of this research program and that apportionment of such payments will be made by the sponsoring companies among themselves.

5. For convenience, the sponsoring companies will designate a person with whom the principal investigator may communicate, and through whom the companies may communicate with the principal investigator, respecting all matters relating to the program.

6. The commencement date of the project shall be September 1, 1972, for the purpose of budgeting. No funds in excess of $200,000.00 which have not been expended or specifically committed for expenditure shall be retained past the end of any fiscal year. In computing the excess amount, any such funds carried forward from a prior fiscal year or years shall be included. If, at the end of a fiscal year, the amount of funds in excess of that figure shall, at the option of Harvard Medical School, be applied as a credit to the next fiscal year or shall be returned to the companies.

7. It is contemplated that at least four associate investigators (e.g., in biochemistry, pathology, physiology and epidemiology), or their scientific equivalents, will eventually be recruited to participate in this program, and that adequate space for their activities will be made available through monies provided by this budget and other-wise. A description of and statement concerning the adequacy of such space shall be provided by the principal investigator to the companies once a year. Such statement shall also include a report on the expenditure and commitment of funds for the preceding twelve-month period.

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8. As the budget indicates, project costs are "direct". All monies contributed will be expended in the furtherance of this program as directed by the principal investigator. A statement certifying that fact will be included in the principal investigator's annual report.

9. With particular reference to the budget item "Alterations and Renovations", any expenditures chargeable to such item shall represent construction or alteration that most effectively implements the project herein described and shall be subject to prior approval by the principal investigator and the sponsoring companies.

The agreement was signed by the following people:

HARVARD MEDICAL SCHOOL

By Gary Huber, M.D.
Principal Investigator

Henry Meadow
Executive Secretary
Committee on Research and Development

Franklin Epstein, M.D.
Director, Harvard Medical Unit
Boston City Hospital

Accepted:

BROWN & WILLIAMSON TOBACCO CORPORATION
1600 West Hill Street
Louisville, Kentuck 40201

LIGGETT & MYERS INCORPORATED
630 Fifth Avenue
New York, New York 10020

LORILLARD, A DIVISION OF LOEWS THEATRES, INC.
200 East 42nd Street
New York, New York 10017

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PHILIP MORRIS INCORPORATED
100 Park Avenue
New York, New York 10017

R. J. REYNOLDS INDUSTRIES, INC.
401 West Main Street
Winston-Salem
North Carolina 27102

LARUS & BROTHER COMPANY, INC.
TRADING AS THE HOUSE OF EDGEWORTH
Richmond, Virginia

UNITED STATES TOBACCO COMPANY
100 W. Putnam Avenue
Greenwich, Connecticut

AMERICAN BRANDS, INC.
245 Park Avenue
New York, New York 10017

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HARVARD MEDICAL SCHOOL

DEPARTMENT OF MEDICINE

DIVISION OF RESPIRATORY DISEASES
GARY L. HUBER, M.D., CHIEF

BETH ISRAEL HOSPITAL

Mailing Address:

BETH ISRAEL HOSPITAL
330 BROOKLINE AVENUE
BOSTON, MASSACHUSETTS 02215
(617) 735-2391

June 29, 1976

Mr. David R. Hardy, Esquire
Shook, Hardy & Bacon
915 Grand Avenue
Kansas City, MO 64106

Dear Mr. Hardy:

In accordance with our several discussions, I am requesting through you a three-year extension of industry funding for our tobacco research program at Harvard University, to cover the academic years of July 1, 1977 through June 30, 1980. The sponsoring institution, as before, will be Harvard University, and we anticipate no change in the location of the performance of the research work. In my discussions with representative administration of Harvard Medical School, the exact format of the agreement previously used will be required to provide compensation for identifiable indirect costs related specifically to the project. We have previously confirmed by individual correspondence that the sponsoring companies are the sole owners of all equipment purchased in conjunction with this project. I would also ask, in addition, that the ownership of any such equipment purchased, both past and in the future, with tobacco funds be clarified in the formal agreement, as well.

We are requesting an amount of $622,014 for the direct costs of the first renewal year, and a total amount of $1,958,293 for the entire three-year period (budget summary enclosed). As before, payments should be provided in equal semiannual installments, with the apportionment of such payments made by the sponsoring companies among themselves.

We will attempt to develop additional support for this program from alternative sources. To continue the program in the comprehensive depth that we are now approaching, and to maintain it at an optimal level of productivity, our staff investigators have suggested a total budget of $834,154 for the first renewal year and a total amount of $2,487,050 for the three-year period. We are submitting this Fall a

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proposal to the National Institutes of Health for a Project Center Research Program relative to smoking and health. We have been, in the past, highly successful in raising Federal funds for research and it is our hope that the difference in funds needed to develop the program to what we believe to be its optimal depth and the amount we are now requesting from the tobacco industry will become available through NIH funding. For one reason or another, should we not obtain additional funding for this program from sources other than the tobacco industry, it will be necessary for us to reach a decision jointly with our sponsors on either a reduction in our total optimal effort or an increase in the magnitude of our industry support.

It has meant a great deal to me personally, and to the University as well, that we have had in the past unified tobacco industry support in this project; it is my hope that all of the companies now sponsoring this program will continue their participation. For the renewal period I will continue as the Principal Investigator in the project and, as such, will pledge to our sponsors the very best of my abilities to achieve those goals of the program outlined in our initial agreement. I and most of our Harvard faculty participants are committed to this project with the majority of our time and effort. I hope that the tobacco industry will approve our request, and we will continue to do our utmost to further develop and sustain a scientifically objective research program relative to smoking and health, with the goal of providing major contributions toward the solution of some of the questions regarding cigarette smoking.

Sincerely yours,

Gary L. Huber, M.D.

GLH:NM
Enclosure

such payments made by the sponsoring companies among themselves.

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RUSSELL S. NOBLET
LOGAN J. WILSON
STEPHEN D. ALIBER
LEO R. GREYER
PATRICK M. SIRRIDGE
DAVID R. MORRIS
ALLEN S. RUSSELL
LAUREL H. CORN
JOHN R. WEISENFELS
ALLEN R. PURVIS
STEVEN C. PARRISH
RICHARD D. WOODS
LARRY R. O'NEAL
BERNARD V. O'NEILL, JR.
GARY R. LONG
JAMES H. OTTMAN
OF COUNSEL

WASHINGTON, D. C. OFFICE
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1776 K STREET, N. W.
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HARLOW W. COOK
WILLIAM H. HOILES
WASHINGTON COUNSEL

November 8, 1976

Gary L. Huber, M.D., Chief
Division of Respiratory Diseases
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Dear Dr. Huber:

I am pleased to advise you that American Brands, Inc.; Brown & Williamson Tobacco Company; Liggett & Myers, Incorporated; Lorillard, a Division of Loews Theatres, Inc.; Philip Morris Incorporated; R. J. Reynolds Industries, Inc.; and United States Tobacco Company are prepared to make available to Harvard Medical School for the academic year July 1, 1976, through June 30, 1977, additional funds in the amount of $147,000.00. These funds will be made available to you upon sixty (60) days prior written request. These funds are to be utilized for the purpose of supporting a program of analytical tobacco smoke chemistry to provide back-up support for biological research in connection with the existing agreement.

A further additional sum in the aggregate amount of $75,000.00 shall be made available to Harvard Medical School upon sixty (60) days prior written request to help support, in an amount not to exceed $35,000.00, teaching and clinical training at Harvard in the general area of pulmonary medicine (such funds to be used only for salaries of fellows and faculty in the Harvard Department of Medicine who are directly associated in a clinical or training capacity with the Smoking and Health Research Program); and to meet in part, in an amount not to exceed $40,000.00, identifiable institutional costs of the now existing program, including certain monies presently claimed to be owed. Such additional sum shall be provided in reliance on and expended in accordance with the provisions of attached exhibits A, B and C.

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SHOOK, HARDY & BACON

The funds to be paid hereunder shall be subject to the terms of the 1972 "Harvard Research Proposal" as amended by the proposed extension agreement enclosed, which must be executed prior to any requests for such funds. A copy of the extension agreement has been sent to Mr. Henry Meadow with the enclosed cover letter.

Sincerely,

William W. Shinn

WWS/rf

Enclosure

cc: Mr. Henry C. Meadow

[illegible] agreement.

[illegible] $[illegible] [illegible] prior written request to help support, in an amount not to exceed $36,000.00, teaching and clinical training [illegible] Department [illegible] Harvard Medical School funds [illegible] salaries of fellows and faculty in the Harvard [illegible] Medicine who are directly associated in a clinical [illegible] program [illegible] and dealin research pro- [illegible] in part, in an amount not to exceed $[illegible] [illegible] institutional [illegible] the [illegible] program, [illegible] monies presently claimed to be owed. Such [illegible] shall be provided in reliance on and expended in accordance with the provisions of attached exhibits A, B and C.

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HARVARD MEDICAL SCHOOL

DEPARTMENT OF MEDICINE

DIVISION OF RESPIRATORY DISEASES
GARY L. HUBER, M.D., CHIEF

BETH ISRAEL HOSPITAL

Mailing Address:

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BOSTON, MASSACHUSETTS 02215
(617) 735-2381

November 5, 1976

William Shinn, Esquire
Shook, Hardy & Bacon
915 Grand Avenue
Kansas City, Missouri 64106

Dear Mr. Shinn:

Relative to our discussions on the awarding to Harvard Medical School supplemental funding in the aggregate amount of $75,000 for the academic year July 1, 1976 - June 30, 1977, these monies will be expended by the Beth Israel Hospital, in an amount not to exceed $40,000, to meet, in part, identifiable institutional costs of the now existing program, including the following program-related direct capital construction costs:

Direct Capital Construction Costs

1. Clifford Douglas Stewart Associates: Architectural Services. Paid by and currently owed to Department of Medicine $2661.92

2. Outstanding renovation bills paid by Beth Israel, but not yet reimbursed to the Hospital by Harvard:

HEW Construction Co.	3883.15
Walsh Brothers, Inc.	4200.00
Clifford Douglas Stewart Ass.	1499.68
	$12,244.75

The remaining $27,755.25 may be used by the Beth Israel Hospital to meet identifiable indirect costs provided they relate specifically to the Tobacco and Health Research Program, and are identified, requested and approved by me prior to disbursement.

The remainder of the supplemental funds, not to exceed $35,000, is to be used to help support teaching and clinical training at Harvard in the general area of pulmonary medicine, with such funds to be used only for salaries for fellows and faculty in the Harvard Department of Medicine who are directly associated in a clinical or training capacity with the Smoking and Health Research Program.

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It is my understanding that the Grantors will make no additional funds available under any circumstances for supplemental direct project costs or indirect costs for the now-funded program. I have been given assurance that the Beth Israel Hospital accepts these expenditures of supplemental funds, that there are not additional invoices outstanding to date in the Department of Medicine for which payment has not been approved and that there will be no further requests relative to the now-funded Tobacco and Health Research Program for additional augementation of indirect costs or other direct costs identified to date.

My warmest personal regards
and highest respect,

Gary L. Huber, M.D.

GLH/th
cc: Mr. Meadow
Dr. Rabkin
Dr. Epstein
Mr. Uris

1003535610

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VARD MEDICAL SCHOOL

BETH ISRAEL HOSPITAL

DEPARTMENT OF MEDICINE
DIVISION OF RESPIRATORY DISEASES
GARY L. HUBER, M.D., CHIEF

Mailing Address:
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330 BROOKLINE AVENUE
BOSTON, MASSACHUSETTS 02215
(617) 735-3291

November 22, 1976

MEMORANDUM

RE: SMOKING AND HEALTH RESEARCH PROGRAM EQUIPMENT

TO: MR. SHINN

FROM: DR. HUBER

I would like clarification of the ownership and use of equipment purchased with funds provided by the grantors to the Smoking and Health Research Program.

As you know, we have variable amounts of support from non-tobacco related research. Sponsors for these programs range from Federal agencies to the private sector.

In addition to our research activities, several of us in the Smoking and Health Research Program who have clinical interests within the hospital and medical school have been asked to provide guidelines for the use of equipment in support of patient related activities.

To help us resolve, for the present and the future, any questions or potential conflicts related to ownership and utilization of the Smoking and Health Research Program equipment, would you please respond specifically to the following points: (1) ownership and utilization of equipment generally, (2) use of equipment in other research programs not funded by the tobacco industry and (3) use of equipment for non-project-related clinical services in the hospital.

I do hope you can clarify these matter in the spirit of those goals for which the grantors established the program.

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1770 R STREET, N. W.
WASHINGTON, D. C. 20006
(202) 331-0757

November 24, 1976

Gary L. Huber, M.D.
Chief, Division of Respiratory Diseases
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Dear Dr. Huber:

This is in response to your memorandum of November 22, 1976:

(1) Equipment ownership and utilization. All equipment purchased with grantors' funds is the exclusive property of the grantors and shall be used only for purposes of the research funded by grantors (The Harvard Smoking and Health Research Program).

(2) Other research. The grantors would agree, I believe, to your having the option of, and responsibility for, utilizing equipment on a temporary basis in conjunction with your other research programs as long as the grantors were assured that such utilization in no way conflicted with nor impeded the research funded by grantors.

(3) Clinical services. I am also of the opinion that the grantors would agree to the occasional use of equipment by you or others participating in the Harvard Smoking and Health Research Program for specialized tests needed in connection with clinical activities provided such utilization of equipment did not in any way detract from nor impede the research funded by grantors.

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SHOOK, HARDY & BACON

I hope that this is helpful to you. I have sent a copy of your memorandum and this letter to the grantors.

Sincerely,

William W. Shinn

WWS/rf

1003535613

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ARVARD MEDICAL SCHOOL
25 SHATTUCK STREET
BOSTON, MASSACHUSETTS 02115
XXXXXXX
732-1495

OFFICE OF THE DEAN

February 8, 1977

William W. Shinn, Esq.
Shook, Hardy & Bacon
915 Grand Avenue
Kansas City, Missouri 64106

Dear Mr. Shinn:

As we agreed over the telephone, I am returning herewith, duly executed on the part of the University, three copies of the Extension Agreement in connection with the Tobacco Research Program. In addition, I am enclosing letters from the Beth Israel Hospital to the Medical School agreeing on the part of the Hospital that they will not look to the School nor to the Tobacco companies for the recovery of indirect costs and that the funds available for project costs will be used for direct costs. In addition, the Hospital agrees that the ownership, use, and custody of equipment acquired through the program will be handled in accordance with your letter to Dr. Huber, dated November 24, 1976.

The Medical School subscribes to both statements. The Medical School will not look to the Tobacco companies for recovery of indirect costs in relation to this program and the funds available for project costs will be used for direct costs. The equipment, with respect to ownership, use, and custody will be handled in accordance with your letter to Dr. Huber, dated November 24, 1976.

If there are other questions or problems, please do not hesitate to let me know.

Sincerely,

Henry C. Meadow
Senior Associate Dean
for Administration

HCM:FD

Enclosures

1003535614

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MITCHELL T. RABKIN, M.D.
General Director

Beth Israel Hospital

330 BROOKLINE AVENUE · BOSTON, MASSACHUSETTS 02215

8 February 1977

Mr. Henry C. Meadow
Senior Associate Dean
Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

Dear Henry:

In connection with the Harvard Smoking and Health Research Program, pleased be assured that the ownership, use and custody of equipment acquired through that program will be handled in accordance with the letter from Mr. W. W. Shinn to Dr. Gary Huber dated 24 November 1976.

With best wishes,

Sincerely,

Mitchell T. Rabkin, M.D.
General Director

lld
cc: Mr. Eugene C. Wallace

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March 9, 1977

Gary L. Huber, M.D.
Chief, Division of Respiratory Diseases
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Dear Dr. Huber:

I enclose a copy of the executed agreement and my letter to Mr. Meadow. Copies have been sent to the participating companies and to Horace Kornegay. I also distributed the Dean's Report.

Sincerely,

Bill Shinn

William W. Shinn

WWS/rf
Enclosure

100353616

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

HARVARD SMOKING AND HEALTH RESEARCH PROGRAM - EXTENSION AGREEMENT

In 1972, a commitment was made by the undersigned Grantors to provide funding for a Smoking and Health Research Program developed by Harvard Medical School. Pursuant to the provisions of the commitment, funding would expire in 1977. However, the undersigned Grantors and Harvard Medical School wish to provide further funding of the program for the three (3) academic years of July 1, 1977, through June 30, 1980, as follows:

1. Grantors shall provide additional monies in the aggregate principal amount of One Million Nine Hundred Fifty-eight Thousand Two Hundred Ninety-three and No/100 Dollars ($1,958,293.00) to be applied to the Smoking and Health Research Program for direct costs only. A budget is attached as Appendix A. An additional sum of ten percent (10%) of any semiannual payment made hereunder will be paid to Harvard Medical School as supplemental funds not as project costs.

If, in accordance with paragraph 1 of the original agreement, the sponsoring companies do not approve a substitute investigator, reasonable and necessary expenses required to terminate the work in progress in an orderly but expeditious manner shall be payable from project monies available or to be made available during the current fiscal year. Any monies not required for such purpose shall be held for disposition as directed by the Grantors.

2. Harvard Medical School shall continue to be responsible for the project. This responsibility shall include providing or arranging for adequate housing, services and the like. Harvard Medical School shall determine the proportion of supplemental funds paid by Grantors that should be paid over to any other institution that may be providing for the project and shall pay such amount.

3. All equipment purchased with funds from either the original or the extended grant is and shall be the exclusive property of the Grantors, as they determine their respective interests, and utilization of such equipment shall be only for purposes of the Smoking and Health Research Program.

4. Harvard Medical School shall cause financial records to be maintained respecting all funds made available by Grantors. Said records shall be maintained consistent with generally accepted accounting principles and shall be made available for audit by Grantors' accountants upon reasonable notice from Grantors. Harvard Medical School shall require similar records (and access to them by

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

Grantors' accountants) of any entity to which it disburses funds other than for the sole purchase of equipment and supplies. Grantors shall have a similar right to all records respecting any funds they make available for the present Smoking and Health Research Program.

5. The provisions of the 1972 Harvard Research Proposal Agreement, as amended hereby, shall continue to govern the extended Smoking and Health Research Program, including procedures and funding. In particular, no direct funds are to be expended without the approval of the principal investigator prior to the initiation of said expenditures. A copy of the original proposal is attached to and incorporated into this agreement by reference as Appendix B.

This Extension Agreement shall be dated as of the date the last of the signatories hereto executes it.

HARVARD MEDICAL SCHOOL

DATE: February 9, 1977

By Gary L. Huber M.D.
Principal Investigator

DATE: February 9, 1977

Executive Secretary, Committee on Research and Development, Harvard Medical School

DATE: February 9, 1977

Franklin H Epstein M.D.
Franklin H. Epstein, M.D.
Herrman L. Blumgart Professor of Medicine
Harvard Medical School

THE FOLLOWING ARE EXECUTING THESE PRESENTS AS "GRANTORS":

BROWN & WILLIAMSON TOBACCO CORPORATION

DATE: FEB. 24, 1977

By Ernest Pepples

1003535618

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LIGGETT GROUP INC.
~~LIGGETT & MEYERS INCORPORATED~~

DATE: Feb. 26, 1977

By _____

LORILLARD, A DIVISION OF LOEWS THEATRES, INC.

DATE: Feb. 24, 1977

By _____

PHILIP MORRIS INCORPORATED

DATE: Feb. 25, 1977

By _____

R. J. REYNOLDS INDUSTRIES, INC.

DATE: Feb 24 1977

By _____

UNITED STATES TOBACCO COMPANY

DATE: Feb 26, 1977

By _____

AMERICAN BRANDS, INC.

DATE: March 1, 1977

By _____

100535619

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BUDGET

DIRECT COSTS ONLY

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel	369,714	399,290	430,597
Equipment	24,800	2,000	2,000
Supplies	65,100	69,350	73,785
Travel	11,100	11,500	11,900
Alterations	4,300	-------	-------
Charlesgate	50,000	55,000	60,000
Clinical Services	50,000	55,000	60,000
ıer	47,000	52,010	53,847
Total	622,014	644,150	692,129

THREE YEAR TOTAL $1,958,29

10035356

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

HARVARD MEDICAL SCHOOL

DEPARTMENT OF MEDICINE
DIVISION OF RESPIRATORY DISEASES
GARY L. HUBER, M.D., CHIEF

BETH ISRAEL HOSPITAL

Mailing Address:
BETH ISRAEL HOSPITAL
330 BROOKLINE AVENUE
BOSTON, MASSACHUSETTS 02215
(617) 735-2391

August 10, 1977

William W. Shinn, Esquire
Shook, Hardy & Bacon
Mercantile Bank Tower
1101 Walnut
Kansas City, Missouri 64106

Dear Bill,

Although we have discussed this on several occasions by telephone, as well as with Mr. Lee Stanford of your group, I do not think I have formally requested that we be given permission to transfer en bloc the budgetary supplementary funding that was awarded for the tobacco chemistry research of this past year. The budget that we had initially developed for the supplementary funds is enclosed. In that this program was budgeted and planned for the just now completed academic year, and in that we had been given assurances late last year by Mr. Hardy that the funds would be available, we undertook this work as scheduled and have now completed it. In that the supplementary funding did not arrive, because of a variety of delays, until almost a full year later, it would be easiest, from the standpoint of the Harvard Business Office, to transfer this amount of money directly into the now overexpended accounts. With this communication I assure you that the research for which these funds were intended has been undertaken and successfully completed. If you need any additional assurances or confirmations, either from myself or from Dr. First, please do not hesitate to let me know. I would like your written permission, which I can transmit on to Harvard Medical School, to allow the transfer of $147,000 from the Harvard University Account entitled "Tobacco Chemistry Program" and identified as 60-092-4716-2 to the now existing Tobacco and Health Research Program account at Harvard incorporating the initial agreement funding from September 1, 1972 to August 30, 1977, and identified as account number 60-092-9006-2. If we cannot make this transfer en bloc, it will require our going back over all of the run sheets and purchase orders for the past year and picking out each individual voucher, including the weekly salaries of the employed technical help. That is a significant bookkeeping task, and I hope you will simply accept my recommendation that we transfer these monies, as indicated above. Please advise me as to whether or not you will accept this recommendation.

If there are any questions that I can answer about this, please do not hesitate to call me directly.

My warmest personal regards
and highest respect always,

Gary L. Huber, M.D., Chief
Division of Respiratory Diseases

GLH/ncb
Encl.

1003535621

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

TOBACCO AND HEALTH RESEARCH PROGRAM

BUDGET SUPPLEMENTAL FUNDS

7/1/76 to 6/30/77

10035622

11/76

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

	% Allocation	Amount	Sub Total
PERSONNEL			
Harvard School of Public Health			
1) Melvin First Research Director	10%	2,000	
2) William Hinds Aerosol Physicist	80%	14,200	
3) Otto Grubner Chemist	50%	11,340	
4) Robert Weker Chemist	90%	12,840	
5) Machinist	15%	1,000	
			41,380
Fringe Benefits (18%)		7,448	
			48,828
Harvard Medical School			
1) David Drath Biochemist	75%	18,750	
2) Research Assistant	80%	8,000	
3) G. Clinton Sornberger Biostatistician	45%	9,450	
			36,200
Fringe Benefits (18%)		6,516	
			42,716

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	% Allocation	Amount	Sub Total
Beth Israel Hospital			
1) Gary L. Huber Research Director	15%	None	
2) Administrative Assistant	25%	4,000	
3) John Shea Bacteriologist	85%	10,328	
4) Machine Operator	100%	7,200	
5) Secretary	35%	3,380	
			24,908
Fringe Benefits (16%)		3,985	
			28,893
SUPPLIES			
Animals		6,063	
Animal Care		5,550	
Chemicals, radioisotope		4,500	
Glassware/disposables		4,500	
Replacement parts for instruments		2,700	
Stationery and Telephone		650	
			12,263
TRAVEL		1,300	
			1,300
SPECIAL SERVICES			
Parts fabrication		950	
Printing		350	
			1,300
		TOTAL	$147,000

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

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GARY R. LONG
TIMOTHY A. PRATT
GARY L. WHITTIER

JAMES H. OTTMAN
OF COUNSEL

FRANK P. SEBREE (1854-1940)
SAM B. SEBREE (1886-1958)
EDGAR SHOOK (1894-1970)
DAVID R. HARDY (1917-1976)

September 15, 1977

RECEIVED
SEP 19 1977
Div. of Respiratory Diseases

Gary L. Huber, M.D.
Chief, Division of Respiratory Diseases
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Dear Dr. Huber:

I have discussed your letter of August 10, 1977, with sponsors of the Harvard program and they have no objection to the en bloc transfer described.

Sincerely,

William W. Shinn

WWS/rf

100353625

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

APPENDIX III

A. Student Research Program Synopsis

B. Student Research Program Report

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

STUDENT RESEARCH PROGRAM

Our Student Research Program was initiated in the summer of 1969 when our Respiratory Diseases Unit was still located in the Channing Laboratory of the Boston City Hospital. We at that time had no significant funding for our research activities, and student volunteers were recruited to help us in our laboratory efforts. In that first year we had three student volunteers in Hunter Nicholas, Robert Kass, and Ellen Finder. For interest, Mr. Nicholas graduated two years ago from Princeton University with honors, entered the Harvard School of Public Health as a special student for one year while doing research in our laboratories, and is now a medical student at Boston University. Mr. Kass graduated with honors from Antioch College and is now a Graduate Student in Biostatistics at the University of Chicago. Ellen Finder graduated, while in the program, with honors from Simmons College, went on to graduate from Downstate Medical School in New York and pursue a career as a physician.

Over the nine years that our program has existed we have had a total of 30 student participants. There are probably an additional few others who entered the program but left soon thereafter without sustained involvement. The activities of all students in the program have been confined to tightly-delineated and self-limiting research projects. The efforts of the 30 students have led to a number of literature contributions as both abstracts and papers. From these contributions there has developed a total of 65 scientific presentations to various national and international professional societies, with 36 of these presentations being made by students. Overall the students have presented to a total of 11 different societies, including American Federation for Clinical Research, the American College of Chest Physicians, the American Physiological Society, the American Society of Clinical Investigation and several other groups.

We have had four very successful student participants from the Positive Program sponsored through the NAACP and the Medical Foundation of Boston. Mr. Nicholas, who has been with us for nine years while otherwise a full-time academic student, has five presentations and seven literature contributions. Mr. Carlton McCarthy, who stayed on with us after his initial summer in the Positive Program has 21 total national or international scientific presentations and a number of literature contributions. He is now a graduate student at Yale University.

The support for operating expenses and student stipends in the program has originated from many different sources, several of whom would prefer to remain anonymous or unacknowledged donors. In the first years of the program, participants were not paid for their efforts. In an attempt to realistically help meet the costs of their ongoing education, however, we have now been able to secure support for them. The stipends that we currently provide are generally competitive to what students are paid in other capacities.

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We have not had any special criteria for acceptance into the program. By their seeking us out, there is probably some selectivity generated by the student with an interest in research or science. We have not as yet undertaken a longitudinal followup of program participants, although we do have some preliminary information on most students. Most of the students initially entered the program at a relatively young age, more often than not while still in high school or in their first year or two of college. The vast majority of them had from the beginning some interest in the biological sciences but not specific or major commitments to careers in medicine or biology. The majority of the students have participated in the program for more than one year and by far most of them now have redirected their education toward a major in the medical or biological sciences.

STUDENTS PARTICIPANTS

Boehme, R. F.	Malik, D.
Broderick, A.	McCarthy, C.
Burley, S. W.	Middleton, B.
Calihan, M.	Nicholas, H. A.
Colpoys, M.	O'Connell, D.
Cutting, M. D.	Overson, P.
Finder, E.	Parad, R.
Glucksman, E.	Pollack, C.
Harris, L.	Redder, D.
Hawkins, J.	Segal, F.
Johnson, S.	Slade, J.
Kelly, W.	Sobel, K.
Kendall, L.	Smith, J. C.
Lee, R.	Spencer, N. J.
Levens, D.	Wilfong, R. G.

tions and a number or literature contributions. He is now a graduate student

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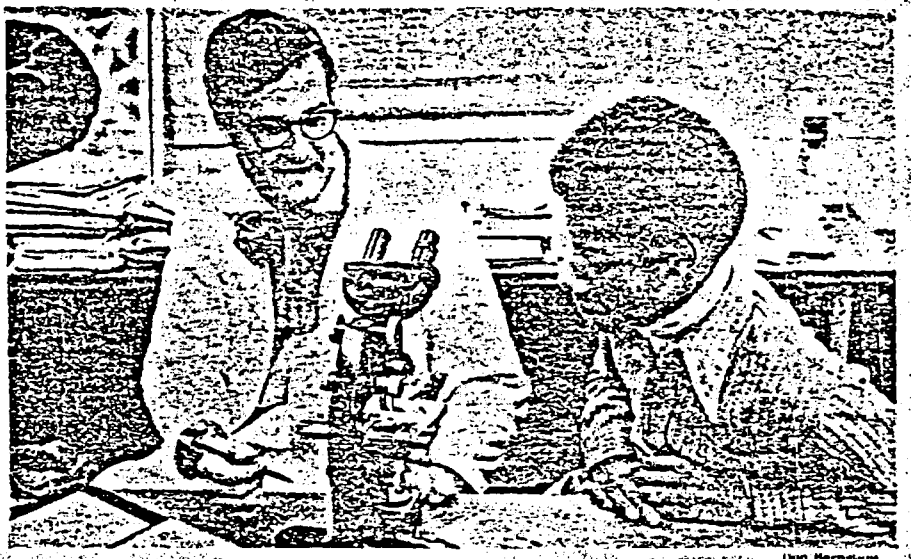
2/6/78

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

EDUCATION

Bucking the System

An outwardly calm medical researcher from Boston walked to the dais of a conference room in a Philadelphia motel one morning last month to discuss "The Effect of Experimental Irradiation on the Anti-Bacterial Defense System of the Lung." His audience was 40 members of the American Federation for Clinical Research. His name was Hunter Nicholas and, at 18, the black researcher from Boston was the first pre-college student ever to present an original paper to the group. Recently, NEWSWEEK's Contributing Editor Joseph Morgenstern interviewed Nicholas and the Boston doctor who started him on his medical research. Morgenstern's report:



Doctor Huber and Hunter Nicholas: Quiet affection and mutual respect

Nicholas is the finest and youngest flower so far of an informal program that was started three years ago at Boston City Hospital by Dr. Gary Huber, chief of Harvard University's pulmonary unit at the hospital's Channing Laboratory for Infectious Diseases. Huber's program doesn't even have a name, let alone a fancy acronym, but its purpose is to expose interested young people to medical procedures and give them positions of genuine responsibility in a research laboratory. The program has no funding and seeks none. It also lacks entrance exams and admission criteria. Huber, as a one-man screening board, looks for motivation, not academic credentials, in the dozen or more teen-agers who volunteer for work in his laboratory each year. "We underestimate what young minds can do," he says. His own motivation is a belief that the fifteen-year grind of conventional medical education can do terrible things to a student's head. "It's a crazy way to train people. You usually put them into a lock step of learning by rote during what ought to be their most creative period."

Hunter Nicholas has never learned the lock step, even though his elementary education was in the same Roxbury ghetto school that Jonathan Kozol made infamous in "Death at an Early Age." When he was 13, his parents realized the inadequacy of his education (his father, a college graduate, is a social worker) and had him bused out of the ghetto to Marblehead High School. He also went to supplementary classes sponsored by his church and the local Boys' Club. At 15, he volunteered for after-school work at a private hospital in Roxbury. "I was the only volunteer there," he recalls, "and I ran around a lot, delivering things. I've always been interested in medicine, whether or not the ambition was clearly formed in my mind. I don't know how it started. It must have been inbred."

Later the same year, Nicholas went looking for more challenging volunteer work at a larger hospital. Boston City sent him to Huber, who had just begun his program for young people in Channing Lab. Huber inflicted a fair amount of scut work on the boy—washing dishes, fetching books and journals from the library—but he also offered work that Nicholas could respect. At 4 a.m. each morning Nicholas came in and injected mice for an experiment the laboratory was running. Huber gave him some medical literature to read for himself, taught him the basics of tissue preparation, assigned him as an assistant to a lab technician and helped him pick a research project of his own.

Elected: None of this went as easily as it sounds, of course. Nicholas needed help in reading and understanding medical terminology. Huber and his lab associates arranged for his enrollment at the Palfrey Street School, a private school in Watertown that counts Robert Kennedy Jr. as one of its students. Palfrey Street took care of his tuition and gave him special tutoring in English and math. Within two years Nicholas had been unanimously elected to the school's board of trustees and was teaching classes in freshman algebra and black literature.

After graduating from Palfrey Street last June, Nicholas delayed his entrance into college, partly in order to finish his research project, an inquiry into the question of why patients undergoing radiation therapy often develop severe and sometimes fatal lung infections. His project was a modest one, carefully delimited in its scope and speculations. It sought to quantify the loss of resistance to infection, rather than to speculate on the ultimate mechanisms of that loss. But any researcher, let alone an 18-year-old, could take professional pride in the work, which involved histology, the use of laboratory animals, statistics, X-rays and radio-labeled bacteria.

When the Boston newspapers learned from a hospital press release that Nicholas was going to present his paper in Philadelphia last month, they dreamed up a familiar kind of hero—the "illiterate ghetto youth pulls himself up from the gutter" cliché. None of the stories even mentioned Nicholas's middle-class background or the intellectual ambitions and traditions of his family. SWEEPER MAKES GOOD, one headline read, even though Nicholas has never, to anyone's certain knowledge, had a broom in his hand. The subject of this nonsense is understandably distressed about it. "The press wasn't interested in my accomplishment," he says. "They were too busy with that stereotype of starting as nothing and then having risen. You know, the rich millionaire who started by shining shoes. That's crap. But, the stereotype says that when you're a black man in the United States you've got to start at the bottom."

Credit: Nicholas and his mentor, Gary Huber, have affection and respect for each other. Huber gives credit where it's due, sometimes to himself and his colleagues for helping Nicholas, more often to Nicholas for the quality and originality of his work. And Nicholas is eager to give credit to Huber's program. "This is really revolutionary, you know, it's really going against the system." And so it is. The system dictates that a medical student do intellectual drudgery for at least eight years, that he delay the beginning of his practice until he's in his mid-30s and overschooled, underexperienced, often exhausted and sometimes only five or so years away from his first heart attack.

The most revolutionary of Huber's notions is that high-school students can do useful, original research, even though their over-all knowledge of medicine may be limited. He feels that Nicholas probably knows more about the effects of radiation on lung tissue than 97 per cent of the doctors in the world. "Getting to be really knowledgeable about a specific aspect of research may involve reading and digesting 50 or so papers. That's a finite number. It can be done. Research isn't all that special," Huber insists. "You don't need the education. You just need to know how to think."

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

APPENDIX IV

HISTORY AND TRENDS OF TOBACCO CONSUMPTION IN THE UNITED STATES

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

TOBACCO CONSUMPTION IN THE UNITED STATES

Historically, the custom of smoking the herbaceous tobacco plant probably originated with the Indians of the Western hemisphere, perhaps as early as 100 A.D., if not before. At first, tobacco was used, as far as we know, principally in connection with religious ceremonies, but by the end of the fifteenth century its widespread consumption had become a common practice throughout most of the hemisphere. Europeans first learned of tobacco smoking when it was observed in Cuba by members of Columbus' crew in 1492. In addition to smoking, the Indians inhaled finely powdered leaves as snuff through a Y-shaped piece of cane, one end of which was placed in a nostril. This instrument was called a "tobago" or a "tobaca," the pronunciation of which was altered by the Spaniards to describe what we now refer to as the "tobacco" plant and its curved leaves.

The first substantial commercial cultivation of tobacco occurred in the New World, when the Spaniards developed tobacco plantations in the West Indies in 1535. Shortly afterwards, it was grown in Spain, as well. Tobacco became popular in Europe for its alleged curative or medicinal powers, usually consumed as a snuff or in the form of poultices. The use of snuff became fashion in the royal court of France, through Catherine de Medici, who used it as a remedy in 1561 at the suggestion of her ambassador to Portugal, Jean Nicot. It was in honor of Jean Nicot that the tobacco plant was later given the botanical name *Nicotinia* and its psychopharmacologically active ingredient called nicotine.

The Spaniards had an essential monopoly on tobacco until 1575, when the Portuguese began to grow large quantities of the crop. Later, Dutch colonists in the East Indies and English settlers in Virginia competed for the European tobacco market, and by the early seventeenth century tobacco consumption was world-wide. Historically, the tobacco trade played an important, if not crucially vital, economic role in the struggle for independence in this country and the establishment of our Republic. It remains, as one of our major exports, an important consideration in our foreign trade balance.

Today, the world production of tobacco is estimated at over a record 11.9 billion pounds, with the largest producers being the People's Republic of China (2.16 billion pounds), the United States (2.12 billion pounds) and, in progressive order, India, Russia, Turkey, Brazil, Japan, Bulgaria, Greece, Italy, Korea and Poland. In the United States, tobacco is grown on about 400,000 individual farms. The farm harvest in this country last year was over one million acres, with an average yield of 2,032 pounds per acre. Tobacco growing requires considerable labor, with over one-half million farm families directly and indirectly involved in producing tobacco in this country. It is that labor force that constitutes the primary political power base in Congress. Up to 300 man-hours of labor are needed to produce and market one acre of tobacco (about 100 times that required for an acre of wheat). Tobacco is the fifth largest American crop (behind corn, soybeans, wheat and cotton), and represents four percent of all cash crops ($2.3 billion for the tobacco-growing farmers).

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

implementing through statistical associations a link of cancer, chronic lung disease, and cardiovascular disease with cigarette consumption. In 1962, the Advisory Committee on Smoking and Health to the Surgeon General of the United States was formed to evaluate the literature of the scientific evidence linking smoking to these diseases up to that time. In its report in 1964, the conclusion of that Committee was that: "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."

With the publicity surrrounding that first report to the Surgeon General, there occurred what at first glance appeared to be a significant reduction

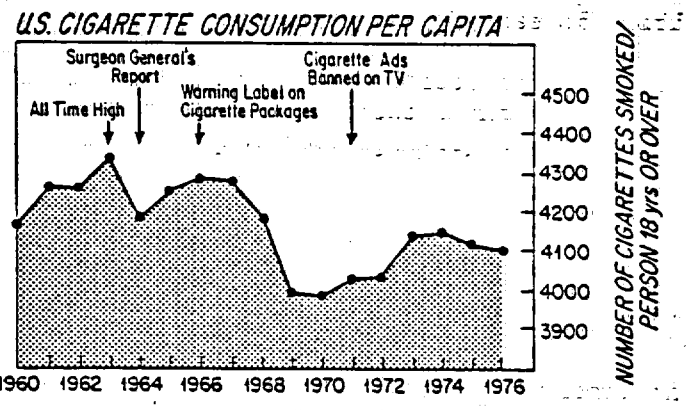

Figure IV-1: Per capita consumption of tobacco cigarettes in the United States adult (18 years of age and older) population, with timing of health warnings and measures.

in per capita cigarette consumption (Figure IV-1). More recent reports from the National Center for Health Statistics and a survey conducted for the National clearing House for Smoking and Health suggested, as quoted in a later supplement of the report on the Health Consequences of Smoking to the Surgeon General, that, "During the past few years, a sharp reduction has taken place in the cigarette smoking habits of the U. S. population." When presented in 1970 that statement, indeed, may have been true, for that year represented a "recent low" per capita consumption of 3,985 cigarettes per population 18 and over.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

A number of regulatory steps on cigarette advertising and sales, including a number of health warnings and measures, have been undertaken over the past 15 years since the first convening of the Committee to the Surgeon General (Figure IV-1). In 1963, the cigarette manufacturers stopped all promotions of their products on college campuses. In 1964 the first report to the Surgeon General was published and updated revisions have been assimilated at regular intervals since then. By 1966, a warning label to the consumer was required by law on the packages of all cigarettes sold, although the industry had agreed to do that on a voluntary basis prior to the legislative requirement. In 1969, the tobacco industry volunteered to stop all advertising on radio and television, and soon thereafter this practice also became law by legislation. In 1970, the cigarette companies voluntarily began to include Federal Trade Commission "tar" and nicotine ratings in advertising. In 1971, the companies added the Surgeon General's warning to its advertising, and this practice became law via the FTC's order to include the warning in all newspaper, magazine, billboard and other advertising. In addition to these measures, the National Clearing House for Smoking and Health, as well as many medical and health organizations and professional societies, have mounted over the years relatively massive anti-smoking campaigns and endeavors. When placed in the perspective of American tobacco consumption over the past three-quarters of a century (Figure IV-2), however, "sharp reductions" in per capita consumption (as noted in Figure IV-1), became relatively less significant. The per capita consumption last year of 4,110 cigarettes per population over age 18 is down really only about 5% or so from the absolute all time 1963 high. There has been a progressive, slow general upward trend over the past eight years from the modern low of 1970. It is unclear that the current estimate over the past year or so of a "net rate of increase" of "zero percent" represents a change in the overall trend, the first step in a reversal or reduction in tobacco cigarette consumption, or simply a "saturation level" for American consumers. With between 50 and 55 million Americans now smoking, it seems small fluctuations in the past 15 years are actually rather minor when viewed in the perspective of tobacco consumption since the turn of the century.

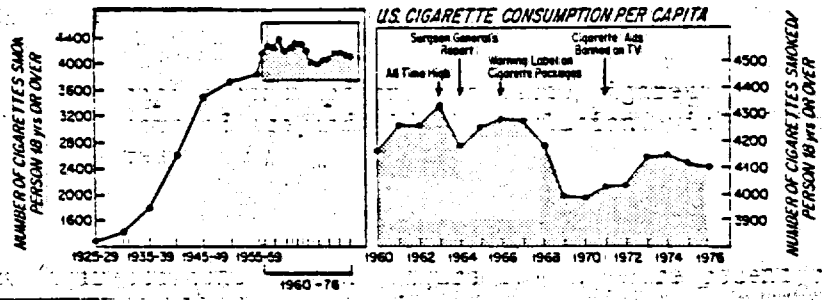

Figure IV-2: Per capita tobacco cigarette consumption in the United States for the adult population, with recent (1960-1976) fluctuations reviewed in the perspective of smoking patterns of the past 50 years. Data for 1977 are not yet readily available.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

Consumption of tobacco cigarettes increased rapidly in this country over the first half of this century. Production and consumption have continued to increase, with small variations, over the past 20 years (Table IV-1). The all-time per capita high was in 1963, with at that time 4,345 cigarettes consumed per adult person in the United States. The current cigarette consumption remains high, along with 5.4 billion large cigars and cigarillos, 2.2 billion small cigars, almost 60 million pounds of pipe and "roll-your-own" tobacco, 84 million pounds of chewing tobacco, and about 26 million pounds of snuff. The output from American factories was a record 693.4 billion cigarettes on the last available figures, with the difference between total production and United States consumption being sent to our overseas armed forces, shipped to other foreign outlets, or stored as industrial inventory.

TABLE IV-I

TOBACCO PRODUCTION AND CONSUMPTION

Year	Output	Domestic Consumption
1955	412.3	382.1
1956	424.2	393.2
1957	442.3	409.4
1958	470.1	436.4
1959	489.9	453.7
1960	506.9	470.1
1961	528.3	488.1
1962	535.5	494.5
1963	550.6	509.6
1964	539.9	497.4
1965	556.8	511.5
1966	567.3	522.5
1967	576.2	527.8
1968	579.5	523.0
1969	557.6	510.5
1970	583.2	532.8
1971	576.4	528.9
1972	599.1	551.0
1973	644.2	590.3
1974	635.0	576.2
1975	651.2	588.3
1976	693.4	617.9

The use of tobacco has always been controversial. In its early history, royal prohibitions, in some kingdoms, forbade the use of tobacco and implemented punishments that ranged up to the death penalty for a third offense. Bans on smoking have been enforced by some religions, and its use viewed with disapproval by many others. Early suggestions on potential health hazards of smoking began to surface in the 1920's. The first major health warnings on tobacco smoking, however, were presented in early 1950's, with the publication at that time of four major retrospective studies on smoking habits of lung cancer patients. Other epidemiologists followed these retrospective inquiries with prospective studies and investigations with a more extensive base, again

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

In summary, then, Americans have been fully warned and informed of smoking-related health hazards, and people continue to smoke at just about the same rate. We know of little evidence to suggest that the latest anti-smoking endeavor initiated by the current Secretary of the Department of Health, Education and Welfare will be any more successful than the many past attempts. Therefore, we believe, better answers are needed, and those can best be obtained through better research.

An extensive review of the published literature implicating the health hazards of smoking is beyond the scope of this presentation. That task has been repeatedly undertaken through the publication of the initial report of the Committee to the Surgeon General and several subsequent updates and revisions of that report, as well as through many additional publications and reviews. From these reviews, however, it is evident that, when based on epidemiologic associations and a variety of carefully controlled experimental studies as well, there exists a relationship that the incidence of disease risk or injury is directly increased as the individual's consumption is increased, and as consumption is decreased the risk of disease is reduced. More often than not, such estimates of dosimetry for the cigarette consumer have been based on the number of cigarettes smoked, either on a "per day" basis or in terms of total "pack-years" of consumption. Equally important is a consideration of the nature and amount of the smoking product delivered from the pyrolyzation of each cigarette. In this regard, much attention has recently been given to the "tar" delivery of cigarettes, and to the trend of lowering "tar" delivery of the smoking products available on the American market. In the phraseology of the smoking and health program of the National Cancer Institute, this has been referred to conceptually as the "less hazardous" cigarette.

Many of the reports by which tobacco cigarette smoking has been linked to adverse health have been based on studies wherein the population evaluated was consuming or had historically consumed a much different cigarette than is consumed in the United States today. In the twenty-year period from 1955 to 1975, there has been a drop in "tar" delivery from 43 mg per cigarette to 18 mg per cigarette. This reduction has come about primarily through a trend by American consumers away from non-filtered to filtered cigarettes. In 1977, only a little more than 10 percent of the American market was comprised of the primary non-filter cigarettes, as shown in Table IV-2.

TABLE IV-2

LEADING NONFILTER CIGARETTES

Cigarette	U.S. Market (%)	Tar (mg)	Nicotine (mg)
Pall Mall	5.0	26	1.6
Camel	3.0	25	1.6
Lucky Strike	1.0	24	1.4
Chesterfield	0.7	24	1.4
Philip Morris	0.3	20	1.1
	10.0% total	23.8 mg average	1.4 mg average

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By contrast, as shown in Table IV-3, almost a third of the market is made up of four leading brands, all of which are filtered, and all of which represent a significant reduction in total tar and nicotine delivery.

TABLE IV-3

LEADING FILTER CIGARETTES

Cigarette	U.S. Market (%)	Tar (mg)	Nicotine (mg)
Marlboro	12.0	17	1.0
Winston	9.2	19	1.2
Kool	6.5	17	1.3
Salem	4.1	18	1.2
	31.8% total	17.8 mg average	1.2 mg average

Of greater interest, perhaps, is the more recent advent over the past two or three years "low-tar" and "ultra low-tar" cigarette, the leading brands of which are presented in Table IV-4. The market for these "low-tar" products is growing, but at such an unstable rate, and with multiple new brands introduced regularly not on the market, that percentage sales are outdated soon after they are compiled. It is estimated, however, that now over 20%, and perhaps approaching as much as 25%, of the American market is made up of "low-tar" projects.

TABLE IV-4

LEADING LOW TAR AND ULTRA LOW TAR CIGARETTES

Cigarette*	Tar (mg)	Nicotine (mg)
Low tar		
Vantage filter	11	0.7
Kent filter	8	0.6
Winston lights	12	0.9
Salem lights	11	0.8
Marlboro lights	12	0.7
	10.8 mg average	0.74 mg average
Ultra Low tar		
True	5	0.4
Carlton	1	0.1
Now	1	0.1
Decade	5	0.5
	3.0 mg average	0.28 mg average

*Exact percentage of United States market unknown (estimated at 20-25% for all low tar and ultra low tar cigarettes).

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

An extensive review of risk modification by low tar products also is beyond the scope of our presentation. The Third World Conference on Smoking and Health did address itself to this matter, however, as have several other contributors in the past few years. Clearly, if disease incidence or prevalence rates are related to tar delivery per cigarette, and the number of cigarettes smoked per consumer remains relatively constant, then the trend towards lower "tar" cigarettes, and especially towards the ultra-low variations, may well reduce disease risk in the smoking population. There are, however, several significant "ifs" in these assumptions: 1) Are the diseases related to smoking through statistical epidemiologic associations really a function of tar delivery alone? 2) Are other components of the cigarette smoke (especially gas phase components) significant as potential etiologic agents of injury and is their delivery reduced, or perhaps even increased, as "tar" content is lowered on a per cigarette basis? 3) Does the consumer smoke more cigarettes per day as nicotine is reduced along with "tar content? 4) Does the consumer smoke differently as nicotine and tar are reduced, thus potentially exchanging one set of diseases or patterns of disease for another?

When a cigarette is burned, some of the smoke is generated as *sidestream* smoke, which for the most part is released to the environment during smouldering between puffs (a very small amount of sidestream smoke also is drawn into a consumer's puff). The remainder of the smoke, exclusive of an amount that is generated but condenses along the tobacco rod, is drawn through the butt end of the cigarette and inhaled by the consumer as *mainstream* smoke. Regardless of distribution, smoke is composed of an aerosol of *particulate matter* that is dispersed in a *gas* or so-called *vapor phase*. The Federal Trade Commission utilizes the term "tar" in referring, indirectly, the *total particulate matter* generated by smoking a cigarette in a standard way, usually to a given butt length or, in some studies, relative to a given number of standardized puffs. The total particulate matter, as a gravimetric expression, is obtained by passing the whole smoke through an absolute Cambridge-type filter and weighing the collected particulate matter. The FTC uses the word "tar" to express the dry weight of the collected condensate (total particulate matter minus water and nicotine). Tobacco chemists on the other hand, refer to "tar" as a laboratory product obtained by passing cigarette smoke through a cold trap at extremely low temperatures. Thus, the assertion that "tar" is something that is inhaled by human smokers is somewhat misleading.

The laboratory condensate of tobacco smoke is referred to as "tar" because of its dark, viscous appearance. It has been suggested by a number of investigators that compounds present in "tar" have the potential to act as tumor initiators or complete carcinogens. The role of some of these agents in environmental and occupational carcinogenesis has been reviewed, and the potential production of these agents in tobacco smoke has been extensively studied. The results of experimental tests in animals to "demonstrate" cause and effect relationships of these carcinogens have had widely differing results and have been controversial. Actually, some studies have had negative correlations, in part perhaps because the chemical components of "tar" undergo reactions and an "older tar" is different from a "fresher tar", in part because the components of "tar" may differ from the components of the particulate aerosol delivered

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to the respiratory tract of human smokers, and in part because results in laboratory animals cannot always be extrapolated to disease risk in humans.

In spite of these controversies, there has been an effort in this country to potentially reduce the risk to the cigarette consumer through a reduction in "tar" content of the commercial products and, in other countries, as suggested by the report on the health consequences of smoking developed by the Royal College of Physicians, to accomplish this by adding synthetic tobacco substitutes to the final product. As is evident from reviewing Tables IV-2, IV-3, and IV-4, however, a reduction in "tar" content has a resultant comparable reduction in nicotine, which is delivered to the consumer almost exclusively in the particulate phase of the smoke. If one of the primary, but not exclusive, reasons people consume cigarettes on a regular or chronic basis is to accommodate a physiologic nicotine requirement, developed through "dependency" or "addiction" to the smoking product, it is of crucial importance to evaluate the effect of nicotine content on smoking behavior.

Nicotine is the most characteristic product of the tobacco plant, comprising a significant proportion of the tobacco leaf. The genetics of tobacco agriculture, including manipulation of nicotine content have been extensively studied. Considerable interest has recently centered on the potential roles of nicotine as an important factor in the development of atherosclerosis and coronary heart disease. The interest in nicotine has originated, in part, on the basis of its known pharmacologic effects on the heart and blood vessels and, in part, from its relatively high concentration in many cigarette products consumed today. The new low nicotine smoking products that have been introduced into the commercial market further enhance the interest in their "safety" as potentially less hazardous cigarettes. The total amount of nicotine a human smoker might obtain from smoking the more commonly consumed products, however, is relatively high or in the range of 40 µgm per kilogram body weight. Once in the systemic circulation, nicotine is rapidly absorbed by many different tissues and metabolized primarily in the liver into pharmacologically less active products, the most important of which appears to be cotinine. Blood nicotine levels have recently been quantified by various techniques. In most consumers, it appears that the plasma nicotine half life is less than 30 minutes.

The pharmacologic effects of nicotine are much better understood than any potential role this smoke component might have on the pathogenesis of atherosclerosis. In the doses of nicotine obtained in man by smoking, it would appear that the biologic effect reported to date include autonomic stimulation, the release of catecholamines to the systemic circulation from the suprarenal medulla and from cardiac stores. This latter effect may represent a direct effect of nicotine or be mediated indirectly by acetylcholine. Nicotine also exerts its effects on chemoreceptors in the carotid and aortic bodies, reflexively inducing acceleration of the heart rate and an increase in systemic blood pressure. In experimental animals, intravenous nicotine produces similar cardiovascular effects to those encountered in smoking, and results in an increase in myocardial oxygen consumption followed by an augmentation of coronary blood flow. These effects on the myocardium are believed due to the release of myocardial catecholamines by nicotine,

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as they can be blocked by propranolol in the intactdog and by reserpine in the isolated cat heart. When animals have had experimentally narrowed coronary arteries, nicotine has induced an impairment response of coronary blood flow, relative to normal controls. One might summarize the known knowledge about the effects of nicotine on myocardial function by implying that the increase in cardiac work following nicotine administration is accompanied by an inadequate increase in coronary blood flow, especially in the presence of coronary insufficiency.

The effect of nicotine on atherogenesis, per se, is virtually unknown. It is unlikely that human populations can be defined that smoke only one low nicotine commercial product for a sustained period of time, and it appears that this question can perhaps best be answered by experimental tobacco smoke inhalation studies in animals susceptible to developing atherosclerotic plaques.

One of the most important yet most complex questions ever addressed by psychobiologists is the matter of "why people smoke," and that is probably not close to being adequately answered. As a broad generalization, we can state that cigarette smoking is perhaps a final common event resulting from a variety of factors both in the smoker's environment and in his/her internal psychological and physiological states. It would be far beyond our task to review this subject even superficially here. It is in regard to the latter factors, however, involving the psychological and physiological states of the individual, that nicotine becomes an important biopsychologic mediator. The current "jargon" employs the term *dependence*, rather than *addiction*, to describe a smoker's "need" or "requirement" for nicotine intake. The biology and psychology of that dependence have been extensively studied, but are very poorly understood.

Most smokers begin to smoke regularly shortly before, during or immediately after puberty. It is commonly thought, but not uniformly agreed upon, that the initial smoking events form an important source of role-defining behavior, linked in part to a complex set of behavior patterns associated with the transition from childhood to adulthood. In that all adolescents are exposed to a variety of factors which both stimulate and inhibit a tendency to begin smoking, these "external" factors somehow interact with a variety of as yet poorly identified "internal" factors for the acceptance by some and the rejection by others of smoking. Once tobacco smoke is inhaled, nicotine, as a sympathomimetic agent, has a direct physiologic effect on the consumer. In addition, there appears to also be a certain amount of tension-reducing effects of smoking, perhaps mediated via parasympathomimetic activity, initiated by the handling of the smoking product and the oral activity involved.

Usually, but not always, the initial effects of smoking are not especially pleasant to most young consumers. Nicotine has an inherent toxicity of its own, and many of the gas phase components are very irritating, even in extraordinary low concentrations. Continued external forces, via peer pressures and a whole host of other factors, however, leads to continued smoking. A *tolerance* to the toxicity of nicotine, and other potentially irritating smoke components,

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develops in those individuals who continue to smoke. Some people appear to be unable to develop tolerance, and smoking cessation inevitably ensues. The development of tolerance is a prerequisite to the development of *dependence* and the physiologic establishment of the *smoking habit*. The "chemistry" of this process has been studied extensively in man and in laboratory animals, but is not at all adequately understood.

If smoking patterns or behavior change in the consumer as a function of altering nicotine content of the commercial product, then considerable consideration must be given to the potential effects of gas phase components of the smoke generated. Russell and co-workers have recently reported that, in a limited number of sedentary workers studied, changing to low nicotine cigarettes caused an alteration in the usual parameters. The findings of this report have been interpreted to support the view that the smoking behavior of the consumer becomes modified to regulate nicotine intake, with a "suggestion" that "safer" cigarettes might actually not be those of lowest tar (because of the low nicotine) content, but rather cigarettes of higher nicotine delivery. The basis for that "suggestion" is that if a smoker smokes to titrate his/her nicotine requirements, he/she might have an increased adverse health risk by a higher exposure to gas phase projects as a greater number and weight of cigarettes was consumed. The gas phase components of greatest concern appear to be carbon monoxide and some of the highly water-soluble, sulphydryl-reacting cytotoxins.

The interest that has focused on the role of carbon monoxide involves the pathogenesis of coronary heart disease and systemic atherosclerosis. By some standards, relatively high levels of carbon monoxide are found in tobacco smoke. As tar and nicotine levels have been reduced in some of the newer commercial products there has been a disproportionately lesser decrease in carbon monoxide of the final smoke product, especially when tar and nicotine reduction are accompanied by filters employing air dilution. With the most commonly consumed commercial cigarettes, however, carboxyhemoglobin levels may reach ranges of 2 to 10 percent, or as high as 20 percent in some smokers, with a significant variation between individual smokers. The levels of carboxyhemoglobin appear to correlate better, in some human epidemiologic studies, with the presence of coronary heart disease than does the smoking history. This may mean that carboxyhemoglobin (or carbon monoxide) may simply be indicating tobacco smoke consumption and does not necessarily mean that carbon monoxide itself is primarily responsible for the pathogenesis of coronary heart disease specifically or systemic atherosclerosis in general. That dilemma can best be answered by controlled experimental tobacco smoke inhalation studies in laboratory animals susceptible to the development of atherosclerotic plaques.

Associations have also been described between atmospheric carbon monoxide pollution and case fatality rates for myocardial infarction. In patients with exertional angina pectoris, secondary to atherosclerotic coronary heart disease, increasing the carboxyhemoglobin levels, through smoking non-nicotine cigarettes or by other means, resulted in a decreased exercise tolerance. In the absence of nicotine, these alterations in exercise tolerance were believed due to carbon monoxide-induced anoxia in the myocardium, mediated by three

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mechanisms: 1) Increased ventricular work and oxygen consumption secondary to stimulation of the adrenergic system, 2) Diminished myocardial oxygen extraction and 3) A decreased capillary oxygen tension from a "left-ward" shift of the oxyhemoglobin dissociation curve.

There is some evidence to suggest a potential etiologic role for carbon monoxide in the pathogenesis of atherosclerotic lesions. Cholesterol-fed rabbits exposed to carbon monoxide had an increased cholesterol content of their aorta, relative to air-breathing controls. Additional work revealed that rabbits fed normal diets and exposed to carbon monoxide had areas in their heart of partial to total necrosis of myofibrosis and arterial alterations that included endothelial swelling, subendothelial edema and regeneration of myocytes. It was postulated that altered vascular permeability and sequestration of albumin led to morphologic changes indistinguishable from early atherosclerotic lesions. Similar mechanisms linking carbon monoxide to atherogenesis in man have been suggested. Additional data have been presented to support these findings. These conclusions have been significantly questioned by others, however, and the definitive function of carbon monoxide originating from tobacco smoke in pathogenesis of atherosclerosis will require further study in the experimental animal.

In addition to the concern for carbon monoxide, there are other gas phase components both in terms of the host defense system of the lung and in terms of carcinogenesis. Part of the cellular energy required for phagocytosis by the alveolar macrophage, as well as the normal function of ciliated cells, is derived by glycolysis, whereas most of the energy needed for intracellular killing of bacteria is presumably generated by a brief burst of hexose monophosphate shunt activity occurring concurrently with phagocytosis. As Green and others have reported in a series of experiments, results of previous work indicate that cytochrome-linked respiration and oxidative phosphorylation in alveolar macrophages are not impaired by gas phase components of tobacco smoke. In contrast, glyceraldehyde-3-phosphate dehydrogenase in the glycolytic pathway is directly inactivated by these gas phase components. Sulphydryl agents, such as iodoacetate, act as metabolic inhibitors to macrophage metabolism and impair phagocytosis. In a similar manner, cysteine and glutathione, as sulphydryl protectors, inhibit the effect of tobacco smoke on alveolar macrophage phagocytosis. Green and co-workers have postulated that acrolein and acetaldehyde are the most active gas phase components responsible for macrophage cytotoxicity in tobacco smoke, and prolonged experimental exposure of animals to one water-soluble component of tobacco smoke, acrolein, has resulted in impaired intrapulmonary antistaphylococcal activity in the presence of co-existing viral infection. In terms of carcinogenesis, the Leuchtenbergers and associates have also emphasized the cytotoxic nature of some of these gas phase tobacco smoke components.

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APPENDIX V

A. Charlesgate Renovation Recommendations

B. Charlesgate Lease

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MODIFICATIONS TO CHARLESGATE FACILITY

UPPER FLOOR

A. Charlesgate West entrance

1. Modify door and sill to provide rodent-proof closure

2. Reconstruct outer walkway to provide a step up to entrance door and seal reconstruction to prevent precipitation drainage into foundation wall.

B. South office suite

1. Eliminate existing door into south office.

2. Divide south office into two offices with an N-S soundproof partition as shown on plan and install access doors as shown.

3. Provide general office lighting, electrical outlets for lamps and office machines, and all-season air conditioning using normal office supply and recirculation rates.

C. North office

1. Extend partitions to ceiling, provide door to reception area, finish.

2. Same as item B-3.

D. Reception area

1. Construct N-S partition 6-ft. west of Charlesgate West entrance. Partition to contain receptionist's glass window and an access door.

2. Construct N-S partition at the location of the existing west wall of the south office with door to lab area.

3. Same as item B-3.

E. Second floor toilet.

1. Toilet to contain one toilet bowl, one washstand and a mirror.

2. Provide general lighting and normal one pass all-season air conditioning.

3. Use construction materials for floor, walls, and ceiling suitable for toilet room without shower facilities.

F. East lab

1. Provide and install 5-ft. lab hood with discharge to roof through unit exhaust blower. Exhaust capacity, 1,000 efm.

2. Construct chemical storage closet as shown on plan and provide (a) unit exhaust blower with capacity of 2.5 per hour. (b) storage shelves (c) lighting.

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3. Construct floor to ceiling N-S partition between east and west labs with 20% glass panel area.

4. Provide and install 20-ft. of lab bench with sink and cabinets under and over and electric service outlets.

5. Provide normal lab illumination, all-season air conditioning using normal office supply and recirculation rates except minimum supply must be 1,000 cfm to satisfy hood requirements.

G. West lab

1. Same as F-4

2. Same as F-5 except no minimum cfm requirement.

H. Access corridor

1. Construct a floor to ceiling E-W partition extending north wall of south office to change room shown on plan. Partition is (a) to contain 40% glass (b) to be flush on wouth side and coated with plastic surface.

2. Provide normal lighting; no ventilation.

I. Change room

1. Provide two N-S partitions with one 30-inch door with light in each .

2. Provide normal lighting. Ventilation not required.

3. Provide clothing storage racks against north wall.

J. New rodent quarters

1. Remove fire door in south wall and fill opening flush to rest of wall.

2. Install monolithic epoxy floor and baseboards.

3. Replace acoustic tile ceiling with metal panels and flush lighting fixtures capable of being sealed with washable plastic coating. Provide 100 f.c.

4. Provide 15 a.c. per hr. one pass all season air conditioning; introducing supply at ceiling or north portion and removing it via a south wall plenum as in pigeon lab.

5. All walls to be glush, smooth, and coated with washable plastic from baseboards to ceiling.

6. Provide and install 10-ft. lab bench with sink and cabinets under and over.

7. Provide and install convenience electrical outlets at lab bench and at other locations.

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K. Aerosol lab

1. Construct floor to ceiling solid flush partitions for 8X10-I.C. aerosol lab with access door, as shown in plan, and finish with plastic coating.

2. Provide and install normal lab lighting and electrical outlets for instruments.

3. Provide and install 12-ft. of lab bench with sink and cabinets under and over.

4. Provide and install 4-ft. lab hood with individual exhaust blower to roof discharging 1,000 cfm after filtration through an NBS 85 prefilter and a HEPA final filter.

5. Provide 1,000 cfm of all-season air conditioning to aerosol lab, with entire supply exhausted through lab hood.

L. Rodent quarantine facility

1. Construct E-W floor to ceiling, flush, partition with 36-in. door as shown on plan.

2. Replace existing floor covering with monolithic epoxy floor and baseboards.

3. Replace existing ceiling with metal panels and flush lighting to provide 100 f.c. and capable of being sealed with washable plastic coating.

4. Provide and install double glazing of window with inner light built flush with inner wall of room and apply a gray light-reflecting plastic film to entire glass panel.

5. Provide and install 6-ft. of bench with sink and cabinets under and over.

6. Provide and install 15 a.c. per hr. all-season one-pass air conditioning introducing supply air at ceiling of N wall and removing it through a discharge plenum, attached to the S wall.

7. Provide and install convenience electrical outlets.

M. Quarantine lock and change room

1. Construct a N-S floor to ceiling partition with 36-in. door as shown in plan and construct 36-in. door in existing partition to provide access to existing rodent quarter.

2. Provide 5 a.c. per hour supply air to lock but no discharge so that room will always be pressurized relative to rodent quarters and quarantine room by one-pass clean air.

3. Provide and install normal flush lighting.

4. Provide and install clothing storage racks against S-wall.

5. Cover walls, ceiling, and baseboards with washable plastic coating.

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N. Existing rodent quarters

1. Replace existing floor covering with monolithic epoxy floor covering and baseboards.

2. Replace existing ceiling with metal panels and flush lighting to provide loof.c. illumination.

3. Provide double glazing throughout with second panes constructed to be flush with existing interior walls and covered with a gray light - reflecting plastic film.

4. Provide new N-S floor to ceiling partition and elevator lock with double doors as shown on plan.

5. Provide new E-W floor to ceiling partition with double doors as shown on plan, to separate animal quarters from smoke exposure facility and workers' sanitary facilities.

6. Same as J-4

7. Same as J-5

8. Same as J-6

O. Toilets

1. Install a shower in each toilet room with bench and clothing hooks.

P. Stairs

1. Provide and install adequate and accessible lighting for each flight.

2. Recover treads with a non-slip material.

LOWER FLOOR

Q. Lockers and toilets - pigeon facility

1. Construct dual locker-toilet facilities as shown on plan.

2. Same as E-1

3. Same as E-2

4. Same as E-3

R. Storage closet, E-wall

1. Construct storage closet with shelves, hooks and access doors as shown on plan.

S. New E-W partition

1. Construct partition from floor to 8-ft. height from E-wall to west side of stairs with southward return to meet existing equipment room wall, as shown on plan, with doors as indicated.

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2. Construct ceiling, from new E-W partition to S-wall, with adequate strength and smooth surface to support over-ceiling storage up to a uniform of lb./sq. ft. and provide and install a sturdy movable ladder resting on wheels and hung from rail at the top to provide access to storage area.

T. Shop

1. Provide and install split 60-in. door as shown on plan.

2. Provide all-season air conditioning using normal office supply and recirculation rates.

3. Provide 100 f.c. illumination.

4. Provide electrical outlets of adequate capacitu for model shop (small) machine tools.

5. Provide exhaust ventilation capacity of 100 cfm for a soldering and welding bench and discharge air to roof with blower switch at work bech.

6. Install standard tile flooring.

7. Provide and install 24-ft shop bench and storage closet.

U. Office/lab (undesignated usage space)

1. Partition and provide with standard office (a) illumination (b) all-season air conditioning and (c) convenience electrical outlets.

V. Pigeon quarantine

1. Same as J-2

2. Same as J-4 utilizing excess capacity of newly installed pigeon lab HVAC system.

3. Install metal ceiling panels and recessed, flush lights capable of being sealed with washable plaxtic coating. Provide 100 f.c. illumination.

4. Same as J-5.

5. Same as J-6 except install 6-ft. instead of 10-ft.

6. Same as J-7.

W. Enclosed dry storage

1. Provide and install normal storage room shelves and bins.

2. Provide vermin-proof partitions and joinings to floor and ceiling.

3. Provide and install double 6-ft. wide door with lock.

4. Provide and install normal storage room illumination.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

5. No ventilation, flooring, or special wall and ceiling finishes required.

X. Under stairs locker and change room

1. Enclose under stairs area with floor to ceiling partitions.

2. Install dual locker rooms with bench in each.

3. Provide normal locker room illumination, all-season air conditioning flooring, and surface finishes.

4. Provide and install access doors shown on plan. It is intended that access to and from stairs shall be through locker room.

5. Provide and install clothes storage rack against N wall of locker room for visitor usage.

Y. Air compressor/vacuum cleaner enclosure.

1. Provide and install a soundproof and leak proof enclosure around and over existing air compressor and "to-be-installed" central vacuum cleaning system exhauster and dust collector with access door adequate for removing vacuum cleaner dust hopper to outside for emptying.

2. Provide and install sound and vibration suppression mountings for existing air compressor.

3. Provide and install enclosure ventilation system to provide 10 a.c. per hr., by drawing in outside air through an overhead duct running from west window, to bottom of enclosure and exhausting via a mechanical blower from the top of the enclosure to the outside via the same west window.

4. Provide and install normal lighting for maintenance functions.

Z. Lunch room

1. Construct 10x13-ft. lunch room with 8-ft. ceiling, glass wall lights, and access door as shown on plan.

2. Provide and install normal illumination and all-season air conditioning, wall-to-wall carpeting, electrical outlets to service coffee machine, refrigerator, toaster-oven, etc.

3. Provide and install 6-ft. drainboard sink and counter with cabinets over and under.

4. Provide and install "small" refrigerator for human food storage.

AA. Cage washer

1. Provide and install cage washing machine in existing cage wash room. Mr. V. Pochay to select model and designate operating temperature.

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BB Service area - (NW corner)

1. Provide and install electrical and water services along N wall west of

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

lunch room for existing humidor, animal refrigerator, and commercial feed mixer.

2. Provide and install (a) normal illumination for a service area (b) winter heating (c) summer ventilation but not air cooling.

3. Paint all surfaces including floor with washable plastic coatings.

GENERAL

CC. HVAC

1. It is intended that existing all-season central system HVAC units will be utilized in a partial recirculation mode for offices, laboratories, shop, locker rooms, service areas, and lunch room. Each space will be provided with a thermostatically controlled mixing box for temperature control.

2. A new all-season HVAC unit will be provided and installed to produce 72F ± 2° and 50% RH ± 5% year round in the existing rodent quarters, the new rodent quarters, and the rodent quarantine room. Each of these rooms is to have individual one-pass supply and discharge ducts in such configuration that cross circulation from room to room is impossible. In addition, supply and exhaust volumes for each of these rooms must be individually adjustable so as to maintain each space at a predetermined pressure relative to ambient and contiguous spaces. To assure correct temperature, humidity, and pressure, each of the rodent rooms is to be provided with appropriate wall mounted indicating instruments and, in addition, wall mounted pressure indicating instruments are to be installed in change room, lock, and access corridor.

3. Window mounted air conditioners in existing rodent quarters are to be retained and maintained as emergency ventilating and cooling units. One unit is to be piped to supply the new rodent room, one is to be piped to supply the pigeon room, and the third is for the existing rodent room.

and access door as shown on plan.

4. An emercengy gasoline-powered generator is to be provided and installed in the downstairs service area with appropriate manual switching gear to power the three emergency HVAC units noted in 3, above.

DD. Central vacuum cleaning system

1. A Spencer vacuum cleaning system capable of servicing three outlets simultaneously and equipped with centrifugal and fabric dust collectors is to be provided and installed on vibration and sound suppressing mountings within the designated first floor soundproof-enclosure Cleaned exhaust air to be discharged through west window.

2. From central location, convenience outlets are to be provided and installed to all areas based on recommendations of Spencer engineer.

3. Cleaning hoses and attachments are to be provided based on recommendations of Spencer engineer.

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EE. Structural improvement

1. Entire building is to be made rodent- and insect-proof by a careful search for the elimination of all means of access from the outside and concealment inside. Special attention is to be giben to foundation walls, access doors, windows, elevator, floor drains, and building service entries.

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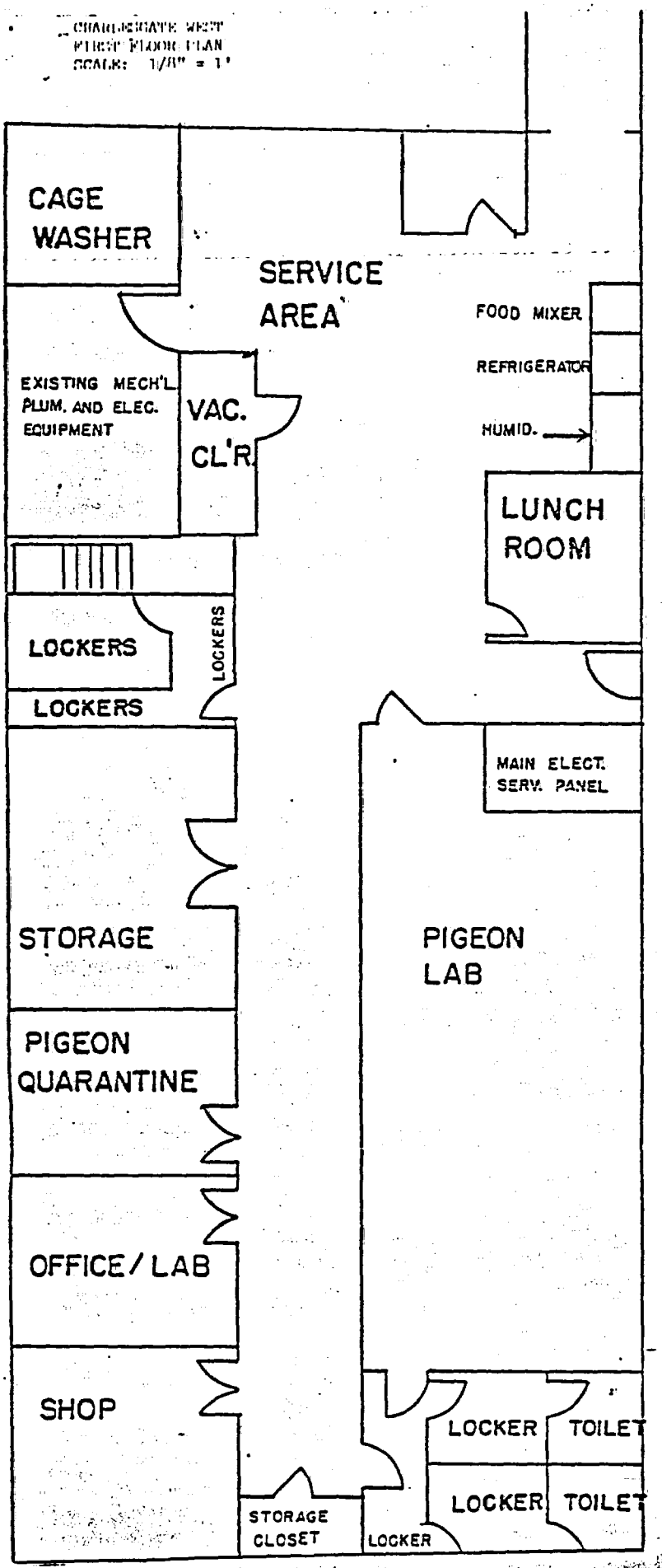
Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

CHARLESGATE WEST
FIRST FLOOR PLAN
SCALE: 1/8" = 1'



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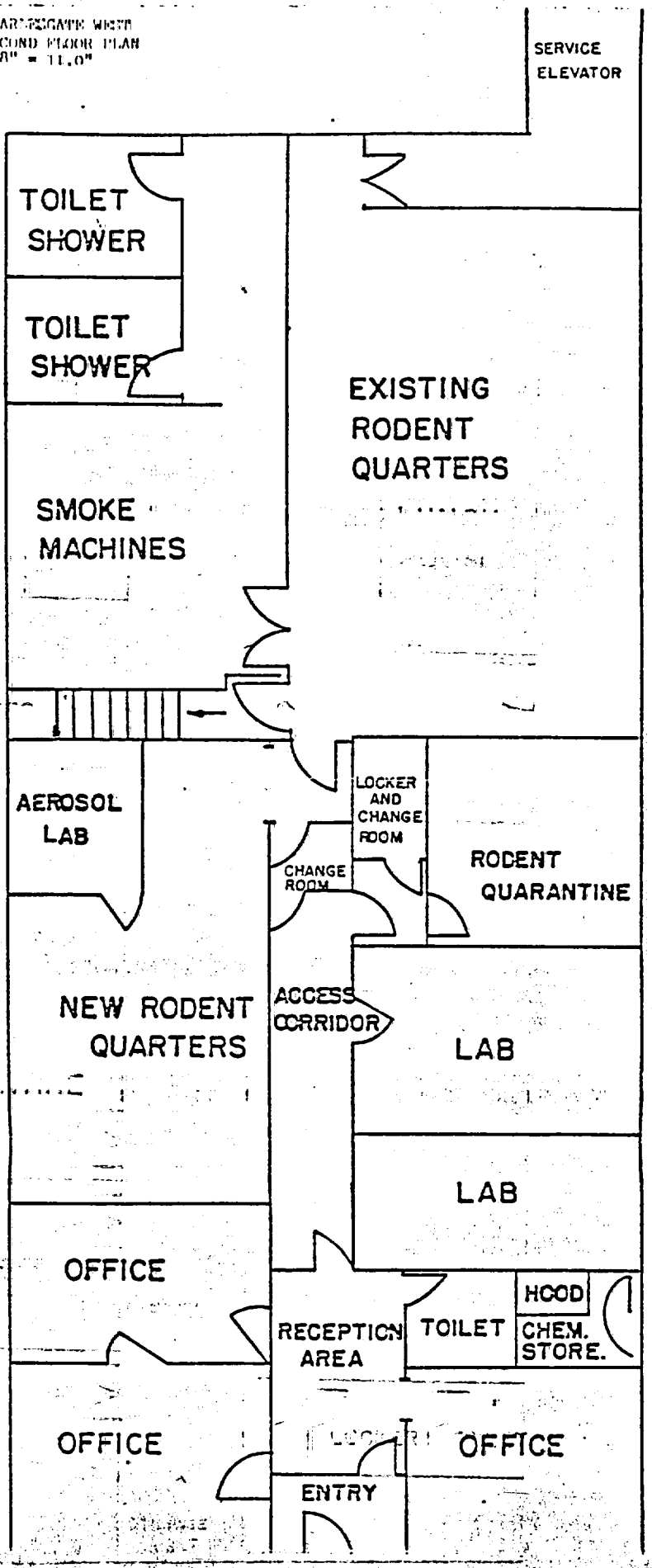
Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

CHARLESGATE WEST
SECOND FLOOR PLAN
1/8" = 1'-0"



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HARVARD UNIVERSITY
SCHOOL OF PUBLIC HEALTH

KRESGE CENTER FOR ENVIRONMENTAL HEALTH
DEPARTMENT OF ENVIRONMENTAL HEALTH SCIENCES

665 Huntington Avenue
Boston, Massachusetts 02115
617-732-1164

October 18, 1977

Dr. Bernard F. Trum
Animal Research Center
Harvard School of Public
Health
Building II, G-9
665 Huntington Ave.
Boston, MA 02115

Gary Huber joins me in thanking you for your kindness in inspecting the animal facility at Charlesgate West and preparing a report of your findings for our guidance.

It is our desire to renovate this building in such manner that it will fully meet Food and Drug Administration, NIH, and Dept. of Agriculture criteria and be eligible for certification should this step become necessary.

In furtherance of this intention we have already removed the rabbits and are planning to follow all of the recommendations contained in your memo of Oct. 13, 1977. In addition, we wish to take advantage of your offer to review our plans and provide continuing advice on our operations.

We are planning to improve the animal facilities further by installing monolithic floors in rooms housing animals, to provide separate quarentine and isolation rooms for pigeons and for rats, to contain feed, bedding, and other supplies in unitized metal containers that are vermin proof and kept in a designated storage area outside the animal rooms, to improve the structure to provide greater protection against vermin and to follow the provisions of Para. 3.c 90, Animal Care, contained on page 51224 of the Federal Register of Nov. 19, 1976.

Would these improvements, in your opinion, provide us with a facility that would meet every one's criteria? If not, would you kindly indicate to me what additional steps should be taken to make the structure and its equipment and facilities of such quality that it will meet the above cited criteria? As I indicated to you earlier today, we are facing an urgent need to define all of the improvements that will be required to make it possible for us to resume full use of the facility for long term chronic studies at the earliest possible date. Your assistance is greatly desired and very much needed. It has been agreed that I will be the individual who will represent the

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interests of the Charlesgate lab for purposes of interacting with you and the Animal Resources Center.

Melvin W. First

Melvin W. First, Sc.D.
Professor of Environmental
Health Engineering

MWF/qrs
cc: G. Huber

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

HARVARD MEDICAL SCHOOL

Memorandum

To: Memo to File

From: Dr. Bernard E. Trum

Date: October 13, 1977

I have visited a research facility (October 3, 1977) operated by the HSPH (Dr. Melvin W. First group representative) at Charlesgate West Research Facility, 6 Charlesgate West, Boston, Massachusetts 02115.

This group operated at the Boston City Hospital until recently and does research on effects of smoke inhalation. They use rats and pigeons almost exclusively, although a few rabbits were on hand.

The facility is a converted office and storage area and, although at the time of visit, was not satisfactory as an animal care facility, both from the standpoint of animal and human health and safety and efficiency of care, it could be made completely satisfactory.

The changes recommended were:

1. Improve ventilation in order to provide adequate air changes (10 to 12 per hour).

2. Do not recirculateanimal colony air. Make up air can be taken from the exhaust of space not used to house animals.

3. Although a single room for rats and a single room for pigeons may be adequate, the control of infectious diseases becomes more difficult. The space between racks must provide the protection that room dividers would ordinarily provide. If the rooms are crowded, an increase in infectious disease must be anticipated. For this reason, it would be preferable to divide the space into as many rooms as practical.

4. Inhalation apparati which were being used are not adequate for the control of disease. A method should be

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devised to sanitize or sterilize the equipment after use before it is used on other animals. If this is not practical, then the number tested on unsanitized equipment should be reduced to the smallest practical and a protocol of use drawn up and followed which will assure that the same equipment is always used on the same animals in the same order of use.

5. The floors should be repaired - the vinyl (tile) floor now in use is adequate provided broken tiles are replaced and the floors thoroughly cleaned and waxed. Dry cleaning of the floor is recommended with a routine disinfection schedule (weekly) followed.

6. Ceilings (tile) are satisfactory provided they are repaired and intact.

7. Walls are satisfactory provided they are intact. The wall-board surfaces do not need resurfacing. A cleanable, hard surface paint should be applied to other surfaces.

8. A rack and cage washer is needed to sanitize equipment to the degree necessary for the control of contagion. This implies the equipment to heat, pump and discharge water which may be adequate, but was not checked. For example, small two-inch sewer pipes below the point of connection, will cause a pressure back up through sinks and toilets above the point.

9. Racks may be hand washed and disinfected regularly without the rack washer, since they do not come in contact with the animals. Therefore, a cage washer would be satisfactory although not as convenient.

10. Storage space for food, bedding and supplies must be provided outside the animal rooms.

The Animal Resources Center (IIMS) will provide a review of plans and advise further regarding the operation of this facility, if requested.

The facility is now regarded as an "off-campus" operation and must comply with the rules for care of animals as approved by the Committee on Animals.

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Having been told of previous difficulties regarding animal health, I strongly recommend that arrangements be made to add a competent comparative or veterinary pathologist to this research facility group.

I must add a disclaimer to this report: The above recommendations, if followed, should result in a satisfactory facility for the research as indicated to me. It will be comparable to facilities on campus, but it will not, however, meet the rigid standards of the "Good Laboratory Practice Act" as required by the Food and Drug Administration.

Bernard F. Trum, D.V.M.

BFT/cs

cc: Dr. Melvin W. First ✓
Dr. Arthur L. Lage
Dr. Harry M. Glass
Col Edwin McMeen
Mr. Ralph H. Charlwood

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WALSH BROTHERS
INCORPORATED
ENGINEERS & CONTRACTORS
BUILDING CONSTRUCTION

TELEPHONES
876-0375
876-0376

150 HAMPSHIRE STREET
CAMBRIDGE, MASSACHUSETTS 02139

December 22, 1977

Gary L. Huber, M.D.
Chief, Division of Respiratory Diseases
Beth Israel Hospital
330 Brookline Avenue
Boston, Massachusetts 02115

Re: Renovations to Charlesgate West

Dear Mr. Huber:

We are pleased to submit our proposal to furnish all of the materials and labor, and perform all of the work required to complete the Renovations to Charlesgate West all in strict accordance with first and second floor plans and specifications received December 5, 1977 for the sum of Three Hundred and Twenty Two Thousand Five Hundred Dollars ($322,500.00).

We have carried as separate items, not included in the above proposal, the following:

Emergency Generator	$25,000.00
Vacuum System	$20,000.00
Sprinklers	$23,000.00

If these items were included in the above proposal the revised sum would be Three Hundred Ninety Thousand Five Hundred Dollars ($390,500.00).

We have included in our base proposal the additional scope of painting, flooring and ceilings in areas such as offices and labs. Also, we have included compressed air and gas in certain areas such as quarantine rooms.

Following is a breakdown of our base proposal:

General Conditions - permit, insurance, temporary facilities, staging, hoisting, supervision, etc.	$20,000.00
General Contractor's Work - rough carpentry, finish carpentry, millwork, interior glazing, mechanical support, cut and patch, etc.	23,300.00
Demolition	3,000.00
Drywall	14,500.00
Masonry	1,000.00
Hollow Metal Frames, Doors & Hardware	9,300.00

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WALSH BROTHERS
INCORPORATED
ENGINEERS & CONTRACTORS
BUILDING CONSTRUCTION

TELEPHONES
876-0375
876-0376

150 HAMPSHIRE STREET
CAMBRIDGE, MASSACHUSETTS 02139

Gary L. Huber, M.D.
Re: Renovations to Charlesgate West (cont.)

Exterior & Interior Windows	$2,500.00
Acoustical Ceilings	5,055.00
Epoxy Floors	7,500.00
Epoxy Paint & Flat Paint	11,545.00
Roofing	3,000.00
Lab Casework & Hoods	25,900.00
Cagewasher	6,000.00
Vinyl Asbestos Tile & Carpet	4,500.00
Toilet Accessories	500.00
Lockers & Shelving	3,300.00
Mechanical Systems	88,000.00
Electrical	31,000.00
Plumbing	30,500.00
Permit	2,100.00
Fee	30,000.00
Total	$322,500.00

It is our suggestion that a contingency of five percent be carried for revisions to scope and latent conditions that may arise during the course of the project.

We thank you for the opportunity to submit this proposal and look forward to being of service to you on this project.

Very truly yours,

WALSH BROTHERS, INC.

by John A. Walsh

JFK/sc

cc: C. Sornberger
M. First

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SUBLEASE AGREEMENT

SUBLEASE AGREEMENT dated as of July 17, 1975, between PITNEY-BOWES, INC., (hereinafter called the Landlord), and THE BETH ISRAEL HOSPITAL ASSOCIATION (hereinafter called the Tenant).

W I T N E S S E T H:

The Landlord hereby subleases to the Tenant and the Tenant hereby hires from the Landlord the premises described as follows:

> The two-story building amounting to 9,000 square feet, in the City of Boston, State of Massachusetts, and located at 6 Charlesgate West, -- hereinafter sometimes called the "subleased premises," being the premises described on Exhibit A.

for the term of two (2) years, to commence on July 1, 1975, and to end on June 31, 1977, both dates inclusive, at the annual rent provided for below, which amount the Tenant covenants and agrees to pay in lawful money of the United States to the Landlord at the office of:

> Field Properties Management
> Pitney Bowes, Inc.
> Walnut & Pacific Streets
> Stamford, Connecticut 06904

in equal montly installments in advance of the first day of each month during said term, provided that no rent or real estate tax payment shall be payable for the month of July, 1975.

The Landlord and the Tenant hereby represent, agree and covenant as follows:

1. (a) The Tenant shall pay rent under this agreement at the annual rate of Twenty Two Thousand Five Hundred ($22,500) Dollars for the first year, and Twenty Seven Thousand ($27,000) Dollars for the second year.

(b) The Tenant shall pay all real estate taxes and assessments against the Leased Premises in excess of $10,740 (1975 taxes for 6 Charlesgate West, Boston, Massachusetts). Each such payment shall be due within ten (10) days of after Landlord notifies Tenant of amount due accompanied by a copy of the paid real estate tax bill. Tenant's obligation shall be prorated for the first and last years of the term.

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(c) The Tenant shall pay for all utilities such as water, fuel and electricity that are associated with the whole 9,000 square foot building, as consumed by Tenant.

2. The rights of the Landlord in respect to the subleased premises derive from the Lease dated March 5, 1963, by and between S. S. Land Corporation, as Lessor, and Landlord, as Tenant,/ (and of the landlord under the Primary Lease), together with Lease Supplement Agreement dated May 24, 1963, and Amendment to Lease Supplement Agreement dated November 30, 1964. During the term of this Sublease, the Tenant shall enjoy all rights of the Landlord under the Primary Lease. A copy of the Primary Lease, Lease Supplement Agreement, and Amendment to Lease Supplement Agreement is attached hereto as Exhibit "B" and the Tenant represents that it has read and is familiar with it.

3. The Tenant shall use and occupy the Subleased Premises only for the purpose of general offices, laboratory and research study.

4. The Tenant shall not sublet or assign the subleased premises or any part or portion thereof without the prior written consent of the Landlord and of the landlord under the Primary lease; provided, however, that no such sublet or assignment shall be deemed to release the Tenant from any of its obligations hereunder; consent to sublet shall not be unreasonably withheld.

5. The Tenant shall improve the premises at its own expense in accordance with approved sketch plans, a copy of which is signed by the parties and annexed hereto and made a part hereof. The improvements shall be made in conformance with all laws, ordinances, rules and regulations of all public authorities having jurisdiction over the premises.

6. The Landlord will not make any modifications to the Primary Lease, or surrender the Primary Lease without the prior written consent of the Tenant, so long as this Sublease shall be in effect. Subject to the provisions of the Primary Lease, and the terms and

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condition of this Agreement, the Tenant shall be entitled to the quiet enjoyment of the Subleased Premises during the term of this Sublease, so long as the Tenant keeps and performs each and every covenant, agreement, term, provision, and condition herein contained or incorporated by reference on the part and on behalf of the Tenant to be kept and performed.

7. This agreement is expressly made subject to all of the terms and conditions of the Primary Lease, and the Tenant hereby expressly:

(a) assumes and agrees to perform all of the obligations of the Landlord pertaining to the Subleased Premises under the Primary Lease to the same extent as if the Tenant had signed the Primary Lease as the Lessee named therein which obligations accrue during the term of this Agreement, and except that the Tenant shall pay rent and real estate taxes only as provided in this Agreement, and for the term provided for in this Agreement; and

(b) agrees to be subject to the same disabilities pertaining to the Subleased Premises to which the Landlord as Lessee under the Primary Lease is subject, except as may otherwise be provided herein; and

(c) agrees to surrender the peaceful and quiet possession of the said subleased premises in the same condition and in as good order as when received, including the removal of new smokestack and restoration of the demisedpremisesin accordance with paragraph 3 of Letter of Consent dated June 1, 1975 from Primary Lessor at the Hospital's expense, upon the Primary Lessor's request, ordinary wear and tear and damage by fire or other casualty excepted. MJTC

8. Tenant covenants that it will occupy the premises in accordance with the terms of the Primary Lease and it will not suffer to be done or omit to do any act which may result in a violation of or default under any of the terms and conditions of the Primary Lease. The Tenant further covenants and agrees to idemnify the Landlord against and hold it harmless from any loss, liability or expense (including reasonable attorney's fees) arising out of,

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by reason of, or resulting from, the Tenant's failure to perform or observe any of the terms and conditions of the Primary Lease relating to the Subleased Premises. Landlord covenants and agrees with the Tenant that this Sublease Agreement will be null and void if Landlord cannot deliver the written consent of the Primary Landlord in accordance with paragraph (3) of the Primary Lease.

9. Notwithstanding any other provision in this Agreement to the contrary, the Tenant shall pay to the Landlord as additional rent any and all sums which the Landlord may be required to pay to its Lessor arising out of, by reason of, or resulting from the Tenant's failure to perform or observe one or more of the terms and conditions of the Primary Lease relating to the Subleased Premises, which accrue during the term of this agreement.

10. If the Tenant shall default in the performance of any of the covenants of this Agreement or shall violate any of the provisions of the Primary Lease, in either case, the Landlord shall be entitled to resort to any applicable remedies herein provided and shall also have the same remedies vis-a-vis the Tenant as the Lessor of the Primary Lease is given by the Primary Lease vis-a-vis the Landlord. The Tenant shall have all the benefits, privileges, powers and rights against the Primary Landlord that the Landlord has against the Primary Landlord under the Primary Lease including but not limited to the work and services to be provided or rendered by the Primary Landlord insofar as the same relates to or affects the Subleased Premises or any part thereof or Tenant's access to or use or occupancy of the Subleased Premises or any part thereof.

11. The Tenant consents, in any action, proceeding or counterclaim brought by either of the parties hereto against the other on any matters whatsoever arising out of or in any way connected with this agreement, the relationship of Landlord and Tenant, the Tenant's use of occupancy of the Subleased Premises, and/or

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any claim of injury or damage, and any emergency statutory or any other statutory remedy, to jurisdiction of any court of record within the City of Boston. If either party obtains a judgement, order or decree in any such proceeding against the Tenant in which the Tenant shall have appeared, the party against whom judgement is made shall pay any expense thereafter incurred by the prevailing party including reasonable attorney's fees, in enforcing or collecting such judgement by any process or proceeding within or without the United States, except expenses in connection with appeals or reargument relating thereto.

12. All notices hereunder shall be in writing. Any notice or other writing to be given or delivered to the Landlord hereunder shall be sufficiently given or delivered if mailed addressed to the Landlord as follows:

Field Properties Management
Pitney Bowes, Inc.
Walnut & Pacific Streets
Stamford, CT 06904

Any notice or other writing to be given or delivered to the Tenant hereunder shall be sufficiently given or delivered if mailed addressed to the Tenant as follows:

330 Brookline Avenue
Boston, Massachusetts

Either party may, by notice in writing, direct that future notices be sent to a different address.

13. The covenants, conditions and agreements contained in this Agreement shall bind and inure to the benefit of the Landlord and the Tenant and their respective legal representatives, successors and assigns, subject to the provision of the Primary Lease.

14. The Landlord shall promptly furnish the Tenant with copies of all notices of default under the Primary Lease as well as defaults under this Agreement which the Landlord shall receive from the Landlord under the Primary Lease or any other party having an interest to which this Agreement is subordinate.

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15. All prior understanding and agreement between the parties are merged with this Agreement, which alone fully and completely sets forth the understanding of the parties. This Agreement may not be changed or terminated orally or in any manner other than by an instrument in writing signed by the party against whom enforcement of the change or termination is sought.

16. The Tenant represents that the Tenant has had no dealings in connection with this Agreement with any brokerage firm or sales representative, other than Maurice diMarco of Julien J. Studley, Inc.,/Realtor, who shall be paid by Landlord.

17. The Tenant accepts the Subleased Premises in "as is" condition, subject to Landlord's representations contained in Paragraph 21.

18. This Lease shall automatically be renewed for an additional three (3) year term, subject to the same terms and conditions contained herein, with the exception of rent, which would be:

$29,700	July 1, 1977 - June 30, 1978
$30,600	July 1, 1978 - June 30, 1979
$31,500	July 1, 1979 - June 30, 1980

provided, however, that Tenant may notify the Landlord sixty (60) days or more prior to the expiration of the present term of its intention to terminate this Sublease.

19. The Landlord represents that as of the date hereof it is not in default under any of the provisions of the Primary Lease.

20. Notwithstanding the provisions of the Primary Lease, in the event that the demised premises are damaged by fire or other casualty or if a substantial portion of the demised premises shall be taken by public authority or quasi public authority and the Landlord or Primary Lessor fails to begin to restore the premises to their condition prior to the casualty within one hundred twenty (120) days after the casualty, then Tenant may terminate this lease by written notice to Landlord within thirty (30) days after said one hundred twenty (120) day period.

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In addition, there shall be an appropriate abatement in rent payable under this Sublease during any period during which all or any part of the demised premises are not usable by Tenant by reason of such casualty or taking.

21. Landlord represents that the elevator and the heating and air-conditioning systems serving the subleased premises comply with applicable laws and regulations.

22. Landlord represents that a notice of the Primary Lease is duly recorded with Suffolk Registry of Deeds, Book Page and that at the request of Tenant, a notice of this Sublease may be recorded at the expense of the Tenant.

23. Where the consent of Landlord is required to any action on the part of Tenant such consent will not be unreasonably withheld or delayed.

WITNESSES:

PITNEY BOWES, INC.

F. A. Groesbeck
Vice President for Administration

WITNESSES:

THE BETH ISRAEL HOSPITAL ASSOCIATION

casualty or if a substantial portion of the demised premises shall

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

THIS LEASE, made this [illegible] day of March, 1963, by and between S. S. LAND CORPORATION, herein called "LANDLORD", and MITNEY-JONES, INC., A BODY CORPORATE, HEREIN called "TENANT".

WITNESSETH, that in consideration of the rental hereinafter agreed upon and the performance of all of the conditions and covenants hereinafter set forth on the part of the Tenant to be performed, the Landlord hereby does Lease unto said Tenant the two-story building amounting to 9,000 square feet, in the City of Boston, State of Massachusetts, and located at 6 Charlesgate West as described and shown on accompanying plat to be Exhibit "A", said property being marked in red, in accordance with the plans prepared by the Architect and Engineer, which said plans have been approved and accepted by the above-named Landlord and Tenant as shown by their acceptance in writing appearing on said plans, for the term of twenty (20) years, beginning on the First day of September, 1963, and terminating on the Thirty-first day of August, 1983, at an annual rental of SIXTEEN THOUSAND EIGHT HUNDRED DOLLARS ($16,800.00), payable in equal monthly installments on the first day of each and every month in advance.

1. The Tenant covenants and agrees with the Landlord without previous demand therefore to pay said rent when due.

2. The Tenant does covenant and agree with the Landlord to observe, comply with, and execute, at its own expense, all laws and valid and lawful rules, requirements and regulations of the United States, State of Massachusetts, City of Boston.

3. The Tenant will occupy the demised premises only for the purposes of an office and service building. The Tenant covenants and

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agrees with the Landlord not to assign this Lease, in whole or in part, or sublet the leased premises, or any part or portion thereof, without the written consent of the Landlord.

4. The Tenant covenants and agrees with the Landlord that the Tenant will not do anything in or about said premises that will contravene or affect any insurance thereon or which the Landlord may hereafter place thereon, and that the Tenant will do everything reasonably possible and consistant with the conduct of Tenant's business, as above limited, so as to obtain the greatest possible reduction in the fire insurance rate of the Landlord on the building hereby leased or of which the premises hereby leased are a part, and upon the request of the Landlord, the Tenant agrees to install such fire pails and fire extinguishers as may be recommended by the Board of Underwriters in order to lower the insurance rate on such building or premises.

5. That the Tenant will not make any structural alteration to said premises without the written consent of the Landlord.

6. The Tenant covenants and agrees with the Landlord to be liable for repairs and maintenance of the interior of the leased premises during the entire term of this Lease, including the heating plant, air-conditioning, bathroom facilities, and all other equipment on said premises, and the parking area, which was furnished by the Landlord, and when vacating, to surrender the peaceful and quiet possession of the said leased premises in the same condition and in as good order as when received, ordinary wear and tear and damage by fire excepted, and the Tenant further agrees that the Landlord shall not be required to render and furnish any janitor services.

7. The Landlord covenants and agrees with the Tenant to make all structural defective repairs on the exterior of the premises whenever

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

the time shall be necessary, ... vidual notice by Registered Mail is given to the Landlord by the said Tenant, and then the Landlord shall have reasonable time in which to make such repairs. If the premises are damaged by fire, the obligation of the Landlord for repairs shall be governed by the paragraph dealing with fire damage hereinafter appearing in this Lease.

8. If the Tenant shall fail to pay said fixed rental or any other sum required by the terms of this Lease to be paid by the Tenant within ten (10) days after the due date thereof, the Landlord shall have the immediate right, without notice, to make distress therefore; and upon such distress, in the Landlord's discretion, this tenancy shall terminate. In case the Tenant shall fail to comply with any of the other provisions, covenants, or conditions of the Lease, on its part to be kept and performed, such default shall continue for a period of ten (10) days after written notice thereof shall have been given to the Tenant by the Landlord then, upon the happening of any such events, the term of this Lease, at the option of the Landlord, shall cease and determine, and for thenceforth, it shall and may be lawful for the Landlord to re-enter into and upon the leased premises, or any part thereof, and to repossess and hold the same as if this Lease had never been executed.

9. It is understood and agreed that in the event the said premises are damaged by fire, condemnation of public authorities, storm, the elements, Act of God, unavoidable accident and/or the public enemy, but not to such an extent as to render same untenantable, then the Landlord shall restore said premises as speedily as possible and there shall be no abatement of rent; and if said premises are injured or damaged by any of the aforesaid causes only to such an extent as to render them partially untenantable the Landlord shall restore such premises so injured or damaged as speedily as possible, rent to abate proportionately on such part of said premises as may have been rendered wholly untenantable until

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such time as such part shall be fit for occupancy, and after which time the full amount rent reserved in this Lease shall be payable as hereinbefore set out. And if said premises are injured or damaged by any of the aforesaid causes to such an extent as to render the same wholly untenantable, then this Lease shall thereupon become null and void, and all liability of the Tenant shall terminate upon payment of all rent due and payable to the date of such happening.

10. In the event of an appointment of a receiver or trustee for the Tenant in any legal proceedings instituted by or against it, including proceedings under Chapters VIII, X, XII, or under any similar provisions of the Bankruptcy Act, if the appointment of such receiver or such trustee is not vacated within thirty (30) days or upon the adjudication in bankruptcy of the Tenant, whether upon voluntary or involuntary proceedings, then any of the said events shall be deemed to constitute a breach of this Lease and thereupon, without entry or other action by the Landlord, this Lease shall become and to be terminated and such termination shall be taken for all purposes, as having occurred at the date of the adjudication in bankruptcy; and notwithstanding any other provision of this Lease, the Landlord shall, upon such termination and as of such date, be entitled to recover, as liquidated damages, an amount equal to the difference between the then present fair value of the remaining rent due under this Lease for the balance of the term and the then present fair rental value of the premises for the balance of the term.

11. The Landlord covenants and agrees that possession of said premises shall be given to the Tenant as soon as said premises are ready for occupancy by said Tenant. In case possession, in whole, cannot be given to the Tenant on September 1, 1963, the Landlord agrees to abate the rent proportionately until possession is given to said Tenant, and the Tenant agrees to accept such pro-rata abatement as liquidated damages for the failure to obtain possession. This provision is placed in this

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Lease so as to evidence the understanding of the Landlord and Tenant that the Landlord shall not be responsible for any delay caused by the enactment of any State, Federal, or local law or by the Promulgation of any Order of the United States Government, State of Massachusetts, City of Boston, restricting building operations or by emergencies beyond the control of the Landlord, strikes, and Acts of God. In the event that possession of said premises is not given to the Tenant and said premises are not ready for occupancy November 1, 1963, the Tenant may at his option cancel this Lease and all agreements pertaining thereto.

12. The Tenant covenants and agrees that it will not place or permit any signs, lights, awnings or poles in or about said premises without the permission, in writing, of the Landlord, and, in the event that such consent is given, the Tenant agrees to pay any sign privilege or other tax therefor. Tenant further covenants and agrees that it will not paint or make any changes in or on the outside of said premises without the permission of the Landlord in writing. The Tenant agrees that it will do nothing on the outside of said premises to change the uniform architecture, paint, or appearance of said building, without the consent of the Landlord in writing, and such approval shall not be withheld unreasonably.

13. The Tenant further covenants and agrees not to pile any goods on the sidewalk in front of said building or block said sidewalk, and not to do anything that directly or indirectly will take away any of the rights, or egress or ingress, of the Landlord or do anything which will, in any way, change the uniform and general design of the property of the Landlord.

14. It is further understood and agreed between the parties hereto that the Landlord shall have the right to place a "For Rent" sign on any portion of said premises for sixty (60) days prior to the final termination of this Lease.

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15. The Landlord shall not be liable for any damage to any property at any time in said or the building arising from fire, or from water, gas, rain or snow which may leak into, or issue or flow from any part of the said building or from the pipes or plumbing or heating apparatus in the same, or from any other place or quarter, or from any other cause.

16. The Tenant covenants and agrees to assume all liability in any action for damages which may arise from any kind of injury to person or property resulting from Tenant's negligence in or upon the Leased premises.

17. It is understood and agreed that the Landlord and its agents, servants and employees, including any builder or contractor employed by the Landlord, shall have, and the Tenant hereby gives them or each of them, the absolute and unconditional right, license and permiss at any and all reasonable times, to enter through, across or upon the premises hereby leased or any part thereof, and, at the option of the Landlord to do such things as are chargeable to the Landlord or to make such changes in said premises as the Landlord may deem necessary or pro

18. It is agreed that the term of this Lease expires on August 31, 1983, without the necessity of any other notice by or to any of the parties hereto.

19. The Tenant covenants and agrees to replace any plate gl which may be broken during its tenancy, at its sole expense.

20. It is agreed for the purposes of any suit brought on ba on this Agreement, this Agreement shall be construed to be a divisible contract to the end, that successive actions may be maintained on said Agreement, and it is further agreed that the failure to include in an

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suits or action any sum or sums then matured shall not be a bar to the maintenance of any suit or action for the recovery of said sum or sums so omitted, and the Tenant agrees that it will not in any suit or suits brought on this Lease for a matured sum for which judgment has not previously been received, plead, rely on or urge as a bar to said suit or suits, the defenses of res adjudicata, former recovery, extinguishment, merger, election of remedies or other similar defense.

21. It is agreed that Pitney-Bowes, Inc., shall have the exclusive use of the entire lot for parking cars in the rear of the building, but the same shall be used for parking purposes only.

22. The Tenant covenants and agrees to pay the Landlord as additional rent, an amount by which the real estate taxes assessed against the demised premises for each year for the term of this Lease exceed FOUR THOUSAND DOLLARS ($4,000.00) yearly; and each such payment shall be due and payable within ten (10) days after Landlord shall have given Tenant notice of the amount due hereunder; and such real estate taxes assessed for the first and last years of the term of this Lease shall be pro-rated.

23. It is understood by both Landlord and Tenant that this Lease shall coincide with the beginning of the Lease for the premises adjoining property located 6 Charlesgate West, better known as the intersection of Charlesgate West and Boylston Streets.

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IN WITNESS WHEREOF the Landlord and Tenant have caused this instrument to be executed by their duly authorized officers and their corporate seals to be hereunto affixed, attested to by their respective Secretaries.

WITNESS:

S. S. LAND CORPORATION

Henry L. Buchan
Secretary

Earle Lipchin, President

PITNEY-AXLES, INC.

C. F. Pollini
Secretary

Vice President

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STATE OF MARYLAND
CITY OF BALTIMORE, to Wit:

I HEREBY CERTIFY, that on this 9th day of March, 1963 before me, the subscriber, a Notary Public of the State of Maryland, in and for the City of Baltimore aforesaid, personally appeared Earle Lipchin, President of S. S. LAND CORPORATION, Landlord, and acknowledged the aforegoing Lease to be the act of the said body corporate.

AS WITNESS my hand and Notarial Seal.

Stanley A. Weinstein
Notary Public

My Commission Expires
5/6/63

STATE OF CONNECTICUT
COUNTY OF FAIRFIELD
CITY OF STAMFORD, to Wit:

I HEREBY CERTIFY, that on this 5th day of March, 1963 before me, the subscriber, a Notary Public of the State of Connecticut, in and for the City of Stamford, County of Fairfield, aforesaid, personally appeared E. M. Bowles of PITNEY-BOWES, INC., A BODY CORPORATE Tenant in the aforegoing Lease, and acknowledged the aforegoing Lease to be the act and Lease of said body corporate, PITNEY-BOWES, INC., Tenant.

AS WITNESS my hand and Notarial Seal.

Mary P. Krause
Notary Public

My Commission Expires

My Commission Expires Mar. 31, 1967

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LEASE SUPPLEMENT AGREEMENT

LEASE between S. S. LAND CORPORATION, Landlord, and PITNEY-BOWES, INC., Tenant; 5th day of March, 1963, as supplemented by Lease Supplement dated [illegible], 1963. Whereas the parties hereto have previously entered into a Lease Agreement under date of March 5, 1963, in respect to the premises known as 6 Charlesgate West, in the City of Boston, State of Massachusetts, as described in Lease Agreement as dated above with accompanying plat, and whereas they have agreed to amend the Lease with respect to the beginning date and termination date, and to confirm the remaining provisions of the Lease in every respect.

NOW THEREFORE, in consideration of the premises and $1.00 paid each to the other, the receipt whereof is hereby acknowledged, the parties agree as follows:

Paragraph 1. That the Lease previously referred to shall be amended as follows:

WITNESSETH, that in consideration of the rental hereinafter agreed upon and the performance of all of the conditions and covenants hereinafter set forth on the part of the Tenant to be performed, the Landlord shall and hereby does Lease unto said Tenant the two-story building amounting to 9,000 square feet in the City of Boston, State of Massachusetts, and located at 6 Charlesgate West as described and shown on accompanying plat to be Exhibit "A", said property being outlined in red, in accordance with the plans prepared by the Architect and Engineer, which said plans have been approved and accepted by the above-named Landlord and Tenant as shown by their acceptance in writing appearing on said plans, for the term of twenty (20) years, beginning on the First day of February, 1964 and terminating on the Thirty-first day of January, 1984, at an annual rental of SIXTY THOUSAND EIGHT HUNDRED DOLLARS

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($10,800.00) payable in equal monthly installments on the first day of each and every month in advance. In the event possession of said premises is not given to the Tenant and said premises are not ready for occupancy April 1, 1964, the Tenant may at his option cancel this Lease and all agreements pertaining thereto.

Paragraph 2. That in all other respects not inconsistent with the above, the aforesaid Lease is hereby confirmed and ratified.

IN WITNESS WHEREOF the Landlord and Tenant have caused this instrument to be executed by their duly authorized officers and their corporate seals to be hereunto affixed, attested to by their respective Secretaries.

Witness:

S. S. LAND CORP.

Secretary

Earle Lupchin - President

ROTHKEY BOATS, INC.

Secretary

Vice President

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AMENDMENT TO LEASE SUPPLEMENT AGREEMENT

LEASE between CHARLESGATE WEST TRUST, Assignee, to S. S. LAND CORPORATION, Landlord, and FITNESS-DUNES, INC., Tenant, 5th day of March, 1963, Lease Supplement dated May 24, 1963, and amended this 3rd day of November, 1964.

WHEREAS the parties hereto have previously entered into Lease Agreement under date of March 5, 1963, in respect to the premises known as 6 Charlesgate West, in the City of Boston, State of Massachusetts, as described in Lease Agreement as dated above with accompanying plat, and whereas they have agreed to further amend the Lease with respect to the beginning date and termination date, and to confirm the remaining provisions of the Lease in every respect.

NOW THEREFORE in consideration of the premises and $1.00 paid each to the other, the receipt whereof is hereby acknowledged, the parties agree as follows:

WITNESSETH, that in consideration of the rental hereinafter agreed upon and the performance of all of the conditions and covenants hereinafter set forth on the part of the Tenant to be performed, the Landlord shall and hereby does Lease unto said Tenant the two-story building amounting to 9,000 square feet in the City of Boston, State of Massachusetts, and located at 6 Charlesgate West as described and shown on accompanying plat to be Exhibit "A", said property being marked in red in accordance with the plans prepared by the Architect and Engineer, which said plans have been approved and accepted by the above-named Landlord and Tenant as shown by their acceptance in writing appearing in

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day of November, 1964, and terminating on the Thirtieth day of November, 1984, at an annual rental of SIXTEEN THOUSAND EIGHT HUNDRED DOLLARS ($16,800.00) payable in equal monthly installments on the first day of each and every month in advance.

Paragraph 2. That in all other respects not inconsistent with the above, the aforesaid Lease is hereby confirmed and ratified.

IN WITNESS WHEREOF the Landlord and Tenant have caused this instrument to be executed by their duly authorized officers and their corporate seals to be hereunto affixed, attested to by their respective Secretaries.

Witness:

LEE R. KOZOL

CHARLESGATE WEST TRUST

Eleanor Thaws, Trustee

PITNEY-BOWES, INC.

P. P. Collins

E. M. Davis
Executive Vice President

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CONSENT

Reference is made to a Sublease dated as of June 1, 1975 between Pitney Bowes, Inc. as Landlord, hereinafter sometimes referred to as the Landlord, and the Beth Israel Hospital as Tenant, hereinafter referred to as the Hospital, relating to premises at 6 Charlesgate West, Boston, Massachusetts.

The Landlord has acquired its interest in the demised premises under a Primary Lease from S. S. Land Corporation dated March 5, 1963, together with Lease Supplement Agreement dated May 24, 1963 and Amendment to Lease Supplement Agreement dated November 30, 1964, all herein called the Primary Lease.

1. Upon the terms and conditions hereinafter set forth the undersigned hereby consents to the Sublease and agrees that:

a. to the best of its knowledge, the Landlord is not in default under the Primary Lease as of this date;

b. any notice of default under the Primary Lease given to the Landlord will be given simultaneously to the Hospital and that during the term of the Sublease the undersigned will accept performance under the Primary Lease from the Hospital for the account of the Landlord.

2. The appointment of a receiver or Trustee for the Landlord, or other event of default under Paragraph 10 of the Primary Lease shall not entitle the undersigned to terminate the possession and rights of the Hospital if the Hospital agrees in writing with the undersigned to perform and observe all of the obligations of the tenant under the Primary Lease for the entire term thereof.

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3. The undersigned hereby consent to the installation by the Hospital at the Hospital's expense, of a new smokestack as described in the drawing by Clifford Douglas Stewart Associates, Architects, 1 Court Street, Boston, Massachusetts 02108, dated June 12, 1975, on the roof of the demised premises, at the side of the building adjoining the demised premises, beside the existing smokestack, to permit emission of smoke from such stack; provided, however, that if requested to do so by the holder of the Lessor's interest under the Primary Lease, Pitney Bowes, Inc. shall at its expense cause to be removed at the expiration or earlier termination of the Sublease, the smokestack installed pursuant hereto and shall at its expense restore the demised premises and said adjoining building to the condition they were in immediately prior to such installation.

4. The undersigned agrees that the Hospital may further sublet or assign the Sublease subject to the prior written consent of the Primary Landlord which will not be unreasonably withheld.

5. By the acceptance of this Consent, the Primary Lease is hereby affirmed. Nothing in this Consent shall operate to release Pitney Bowes, Inc. from any of its obligations under the Primary Lease, and Pitney Bowes, Inc. shall remain liable thereunder.

The undersigned further acknowledges that the Primary Lease is superior to the Mortgage to Malden Savings Bank, Beverly Savings Bank, Essex Broadway Savings Bank, and The Worcester North Savings Institution recorded with Suffolk Registry of Deeds, Book 7937, Page 468.

In addition, the undersigned represents that it is duly authorized to execute this Agreement on behalf of Beverly Savings Bank, Essex Broadway Savings Bank and The Worcester North Savings Institution.

The undersigned further agrees to execute such additional instruments as the Hospital may require to confirm the provisions of this Agreement.

Executed as a sealed instrument as of the 31st day of July, 1975

MALDEN SAVINGS BANK, (in its own behalf and on behalf of Beverly Savings Bank, Essex Broadway Savings Bank and The Worcester North Savings Institution)

BY: _____
Vice President

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APPENDIX VI

A. Tobacco and Health Research Program Organizational Administrational Chart

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ORGANIZATIONAL CHART

HARVARD TOBACCO AND HEALTH RESEARCH PROGRAM

ADMINISTRATION (5)

Huber, M.D.
Share
Levine
Moss
Cooney

BIOSTATISTICS (2)

Sornberger, Ph.D.
Fulchiero

ANIMAL FACILITIES (18)

Pochay
Zwilling
Gugger
Butler
O'Dell
Parkinson
Glennon
Toledo
Abraham
Pollack
Sinclair
Saipe
(Six unfilled)

ANALYTICAL CHEMISTRY (4)

First, D.Sc.
Hinds, D.Sc.
Grubner, Ph.D.
Weker, M.S.

BIOCHEMISTRY (6)

Drath, Ph.D.
Shea, M.S.
Wong
Price
LaBrecque
Simpson

MORPHOLOGY (9)

Davies, Ph.D.
Hayashi, M.D.
Engel
Colpoys
Nauss
Koplin
Miaskiewicz
Nicholas
Avery

PULMONARY PHYSIOLOGY (6)

Mahajan, M.D.
Rubin, M.D.
Goldman, M.D.
Hedley-Whyte, M.D.
Miller, M.D.
Bancroft

CARDIOLOGY (5)

Abelmann, M.D.
Bing, M.D.
Sakuari, M.D.
Stemerman, M.D.
Goldberg, M.D.

CONSULTANTS (7)

Skinner, Ph.D.
Solomon, M.D.
Epstein, M.D.
Hojnacki, Ph.D.
Lage, D.V.M.
Fadoul, M.D.
Wite, Ph.D.

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APPENDIX VII

A. Tobacco and Health Research Program Seminar Schedule

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RESEARCH SEMINARS

TOBACCO AND HEALTH RESEARCH PROGRAM

HARVARD UNIVERSITY

Winter-Spring Schedule

1978

January 12	Pigeon Atherogenesis Model HSPH, Kresge Bldg.	Dr. Huber Dr. First
January 26	Pathophysiologic Mechanism in the Development of Atherosclerosis HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Stemerman
February 9	Rehearsal: Ad Hoc Adivsory Committee Meeting	
February 23	The Role of Tobacco Smoking in the Pathogenesis of Atherosclerosis: Fact and Fiction HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Goldberg
March 9	Quantitative Morphological and Biochemical Analysis of Atherosclerosis in the Pigeon Tobacco Smoke Bioassay Model HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Davies Dr. Drath
March 23	Biochemical Basis for Atherogenesis HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Hojnacki
April 6	The Effect of Tobacco Smoke on Myocardial Metabolism and Function HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Abelmann Dr. Bing
April 20	Respiratory Physiology: An Overview HSPH, Kresge Bldg., Room 101A (Bldg. II)	Dr. Goldman

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May 4	Magnetometric Monitoring of Smoking Profiles for Nicotine Accommodation and Titration in Man HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Rubin Dr. Mahajan
May 18	Immunology of the Respiratory System: An Overview HSPH, Kresge Bldg., Room 101B (Bldg. II)	( )
June 1	Stereology and Metabolism of the Pulmonary Alveolar Macrophage HSPH, Bldg. I, Room 602	Dr. Davies Dr. Drath
June 15	Tobacco Smoke and Chronic Lung Disease in Man and in Animal Models HSPH, Kresge Bldg., Room 101B (Bldg. II)	Dr. Huber

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APPENDIX VIII

A. Smoking and the Nonsmoker Article

B. Editorial

C. Related Correspondences

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

MEDICAL INTELLIGENCE

CONCENTRATIONS OF NICOTINE AND TOBACCO SMOKE IN PUBLIC PLACES

WILLIAM C. HINDS, SC.D.,
AND MELVIN W. FIRST, SC.D.

PUBLIC interest has focused on health effects to the large numbers of nonsmokers exposed to tobacco smoke in public places. Recent regulations in a few cities have banned smoking in public places, or have restricted smoking in the manner of United States commercial aircraft.

Two studies[1,2] indicated that in crowded private rooms concentrations of tobacco smoke often exceed 260 μg per cubic meter, the federal air-quality standard for particulate matter that is not to be exceeded more than one day per year. Hoegg[1] estimated that in residences, meeting rooms, or private automobiles, the nonsmoker inhales in one hour the equivalent of smoking 0.01 to 0.20 cigarettes. Bridge and Corn,[2] by measuring carbon monoxide during party situations involving 50 to 73 people in rooms of 140 and 100 m^3 under controlled ventilation conditions, estimated smoke concentrations to be 2000 to 4000 μg per cubic meter and concluded that these levels are a matter of concern.

Estimation of levels of tobacco smoke in public places was undertaken to evaluate the health implications for nonsmokers. Measurements were limited to the particulate phase of tobacco smoke, although it is known that the gaseous phase also contains substances that may affect health. Since the objective was to measure only tobacco smoke, all methods commonly used to measure total suspended particulate matter were ruled out because of the many other sources of particulate matter in the indoor atmosphere. The use of carbon monoxide as a tracer has similar disadvantages because of the widespread distribution of this common air pollutant. Nicotine was chosen as the tracer for tobacco smoke for the following reasons: it is specific for tobacco smoke (the only other source of nicotine is from agricultural sprays, which are unlikely to be a contaminant of the indoor atmospheres tested); with the exception of water, nicotine is the largest single component of the particulate phase of tobacco smoke; nicotine concentration is unaffected by the moisture content of the smoke; and sensitive gas chromatographic analytical methods are available for measurement of nicotine concentrations.

From the Department of Environmental Health Sciences, Harvard School of Public Health (reprint requests should be addressed to Dr. Hinds at the Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115).

Supported by the Massachusetts Lung Association and its local affiliates.

Because of the wide range of public places evaluated and the small number of samples, the procedures employed and the results should be considered a pilot study having the limited objective of defining the extent of the "passive-smoking" problem in public places.

SAMPLING METHODS

The procedure was to enter a public place as a patron and sample a known volume of air through an AA Millipore filter having a collection efficiency for tobacco smoke greater than 99 per cent. Samples were taken with an inconspicuous battery-powered pump at a rate of 4 liters per minute for a maximum period of 2½ hours. The entire sampling system weighed 1.3 kg and was contained in a phenolic box, 17 by 13 by 6 cm (Fig. 1). To obtain realistic samples, the unit was placed as close to the breathing zone as possible — e.g., on a table in a restaurant, or on a lap in a train.

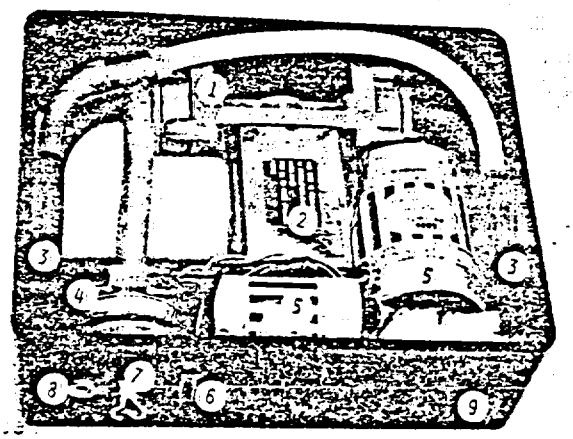

Figure 1. The Sampling System, Showing the Pump (1), Motor (2), Pulsation Damper (3), Filter Holder (4), Rechargeable Batteries (5), On-Off Switch (6), Air Inlet (7), Battery-Charging Jack (8), and Case (9).

The material trapped on the filter was extracted with distilled water, concentrated by rotary evaporation, and analyzed for nicotine with a gas chromatographic technic described by Jacin et al.[3] The nicotine content was used to calculate the tobacco-smoke particulate concentration on the basis of an experimentally determined nicotine fraction of 2.6 per cent established by measurement of total particulate mass and nicotine concentration of sidestream smoke in an aerosol chamber. Sidestream smoke is the principal component of indoor tobacco-smoke pollution (i.e., 80 to 90 per cent).[1,2]

Tests were run with filter and nonfilter cigarettes, and current sales figures[4] were used to calculate the weighted average nicotine fraction as 2.6 per cent. No noteworthy concentration effect on nicotine fraction was observed for smoke concentrations ranging from 6000 to 110,000 μg per cubic meter. Our ambient measurements were an order of magnitude smaller than this range.

Twenty-three samples were taken in the Boston area during 1973 and early 1974. Some types of public areas — commuter trains, commuter buses, and bus and airline waiting rooms — were sampled repeatedly, whereas others, such as large, crowded restaurants and lounges, are represented by individual samples. On buses and trains no attempt was made to sample in smoking or nonsmoking sections because these designations are largely ignored by passengers.

RESULTS

Smoke concentration for each category of public place is shown in Table 1 as weight per unit volume of sampled

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Reprinted from the *New England Journal of Medicine*
292:844-845 (April 17), 1975

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

SMOKING AND NONSMOKERS — WHAT IS THE ISSUE?

With tobacco consumption near an all-time high, a fervent interest has developed over the effect of passive smoke inhalation on the nonsmoker. Controversy exists on the rights of the nonsmoker to "clean" air versus the rights of the smoker to enjoy a product consumed by man for centuries. This issue extends far beyond the health professions and is complicated by the divergent interests of many groups, with approximately 160 proposals to restrict or segregate the smoker now pending before legislatures in 39 states. The primary issue is how much tobacco the nonsmoker passively inhales and what the potential health hazards of such exposure are. The number of publications attempting to answer these questions is very large. Until the contribution by Hinds and First in this issue of the *Journal*, reliable data on relevant public passive exposures to tobacco smoke have been sparse.

When cigarettes are consumed, tobacco smoke is generated in part as mainstream smoke, essentially all of which is actively inhaled and 70 to 90 per cent of which is retained by the smoker. Sidestream smoke of the burning cigarette is the primary source of exposure to the nonsmoker, representing about 50 per cent of the tobacco burned and responsible for approximately two thirds of the aerosol particles delivered to the environment. Smoke contains about 2000 or more identifiable components and can be divided into gas and particulate phases.[1] Ambient concentrations of trace components can be measured, and potential amounts of pyrolized products available for inhalation by the nonsmoker determined.

Using nicotine as a tracer of the particulate phase, Hinds and First have indicated that the nonsmoker can potentially inhale only extremely small amounts of tobacco smoke. Nicotine may be an ideal tracer for such studies, since it is basically unique to tobacco. Other investigations have indicated that nicotine may occur in the urine of nonsmokers in concentrations at approximately 5 per cent that of smokers.[1] Contrary to the conclusions of Hinds and First, this figure suggests a passive consumption by the nonsmoker of about one full cigarette over an hour. These results, however, were obtained under experimentally high concentrations intolerable to prolonged human exposure. Carbon monoxide, a gas-phase component, has been used as a popular alternative tobacco tracer, producing environmental concentrations of 10 ppm or so.[2] For comparison, concentrations of 30 ppm are not uncommon in dense urban automobile traffic, and 100 ppm can be reached in polluted cities with temperature inversions.[2] Regardless of how studies are performed, only limited conclusions can be achieved by employment of tracers.

Definitive answers to questions of tobacco and nonsmokers should be obtained from data demonstrating the presence or absence of potentially associated diseases in man. That kind of information is extremely hard to come by. Potential health effects of tobacco on the nonsmoker have recently been reviewed[3,4] and are summarized as follows. Acute effects of short-term exposure to environmental tobacco smoke in population studies have not been evaluated in adequate depth. No chronic studies have been reported for adults. No data are available to demonstrate health effects of physiologic responses to nicotine levels reached in adult nonsmokers, and carbon monoxide concentrations in nonsmokers are far below levels that are of known health hazard. Potential effects of other smoke components on nonsmokers are conjectural. Information is lacking on cumulative effects of prolonged passive exposure to tobacco-smoke products. Potential additive or synergistic effects of tobacco-smoke products with nontobacco environmental contaminants need to be investigated. Interesting data have appeared, however, to suggest an increasing prevalence of acute respiratory disease in young children whose parents smoke.[5,6] These studies have been criticized because the data are sparse and perhaps influenced by socioeconomic and housing conditions, infections in parents, genetic differences and other factors.[7]

Hypersensitivity reactions to tobacco in the nonsmoker deserve more clarification. Commonly, atopic persons complain that tobacco smoke provokes respiratory-tract symptoms. Many agents in tobacco smoke could theoretically act as haptens and produce immunologic responses after binding to suitable carriers, but there is little experimental or epidemiologic evidence that sensitization to tobacco smoke exists.[8] Fletcher et al., in a report to the Royal College of Physicians of London, concluded that "...there is no evidence that other people's smoke is dangerous to healthy nonsmokers, but it can be extremely irritating and cause distressing symptoms, especially in allergic persons or in those already affected by heart or lung disease."[9]

One is left, then, with a perplexing and unsolved dilemma. The data of Hinds and First demonstrate that in public places nonsmokers could potentially consume 1/1000 to 1/100 of one filter cigarette per hour, a level of exposure that has had no known serious association with disease. Why, then, do so many nonsmokers appear to be adversely affected by passive exposure to tobacco? Perhaps acrolein and aldehydes, present in the smoke, act as irritants in extremely low concentrations and especially affect latently or overtly hypersensitive persons. The odor threshold for stale smoke components, which is also very low, may trigger emotional responses not yet well understood.

Clearly, numerous nonsmokers feel impaired in their well-being if exposed to tobacco smoke. The World Health Organization defines health as a condition characterized not only by the absence of diseases and infirmity but also by the presence of full psychologic, mental and social well-being.[10] By this definition, the nonsmoker passively exposed to tobacco may indeed have an adverse health response on a psychogenic basis. The issue remains unanswered beyond that, and, to solve this problem, scientific contributions in this area should be broadened, thereby diminishing speculation. In developing crucially needed research on this issue, one should identify the compounds of tobacco smoke that provoke adverse reactions in nonsmokers, establish if these reactions are dose

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SMOKE AND HEAT

To the Editor: The article by Hinds and First on tobacco smoke in public places and the editorial by Huber appearing in the April 17 issue of the *Journal* both provided interesting reading on this controversial subject. Unfortunately, their conclusions were disappointing if not unjustified.

Hinds and First thought that the average level of tobacco smoke in public places does not account for the public outcry regarding this problem even though they demonstrated levels exceeding the minimum air-quality standards that are not to be exceeded more than once per year. Does this attitude mean that one should accept indoor air-pollution standards lower than the outdoor standards? After all, an estimated 80 to 90 per cent of one's time is spent indoors.[1]

In the accompanying editorial by Huber, one gets the impression that since there is no overwhelming evidence that smoking is harmful to nonsmokers, one can be passive in one's efforts to discourage smoking in public places. I remind Dr. Huber that the majority of the population does not smoke and should be given the benefit of the doubt regarding its health. The burden of proof that passive smoking is safe for the nonsmoker resides with those who choose to smoke.

Dr. Huber mentioned studies implicating possible dangers to infants of smoking mothers.[2,3] Colley et al. have reported that infants exposed to cigarette smoke have twice the risk of an attack of pneumonia or bronchitis.[4] Colley, in another publication, reported an increased prevalence of cough in children six to 14 years of age whose parents smoked.[5] A third study by Colley et al. showed an increased prevalence in respiratory symptoms in 20-year-old subjects who smoked and had a history of a lower-respiratory-tract infection under the age of two years, both factors being related to parental smoking habits.[6] Others have reported similar findings, as well as the adverse effects on the fetus and an increased neonatal mortality in offspring of smoking mothers.[7-9] Yet another victim of passive smoking is the asthmatic patient, recently shown by O'Connell and Logan to be subject to exacerbations when exposed to tobacco smoke.[10]

Other, less publicized consequences of smoking on the nonsmoker include the shared burden of smoking-related health costs, estimated at 5.3 billion dollars in 1966, and the high job absenteeism associated with smoking.[11,12]

Smoke concentrations in public places probably have an adverse effect on infants and asthmatic persons, and by Dr. Huber's own admission may have an adverse health response on the nonsmoker on a psychogenic basis. It is nearly inconceivable that when enough studies have been done, there will be no long-term ill-effects from passive smoking. While we await the results of these studies, we should spend our efforts in preventive medicine—namely, reiterate the stand against smoking. Hospitals should ban cigarette sales and prohibit smoking on their premises, and health-care personnel should continue their lead in giving up smoking. Reports of such efforts are encouraging.[13]

The answer to Dr. Huber's question about the issue of smoke in public places becomes clear. Since cigarettes cost the nonuser money, may harm his health and are at least obnoxious, the basic issue for the nonsmoker is self-preservation.

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To the Editor: Through the singular smokiness of the editorial entitled "Smoking and Nonsmokers — What Is the Issue?"[1] I see that its writer missed the point: smoke stinks! Nothing escapes the flatulent ambience of smoke: skin, hair, clothing, car, lecture hall, office, restaurant, school, library, museum, elevator, sauna, conjugal bed and all else within puffing radius of those with a proclivity for pollution. The writer of the editorial sees a "perplexing and unsolved dilemma" or even "an adverse health response on a psychogenic basis" because he has confused the health implications of smoke pollution with its aesthetic and legal implications.

The 23 samples from the inconspicuous pump of Hinds and First[2] do not demonstrate "in public places nonsmokers could potentially consume 1/1000 to 1/100 of one filter cigarette per hour." The "equivalent filter cigarettes smoked per hour" is not a bit of measured data; it is an arithmetical gimmick using several statistical assumptions. Consider that 1/1000 of a 100-mm filter cigarette would mean the smoke from less than 1/10 mm of tobacco. I would invite the authors to place that much tobacco on their desks and then to believe that this would be the entire source of the smoke inhaled per hour by nonsmokers in a smoke-filled room. Zeal for numbers seems to have obscured common sense.

Ann Arbor, MI GAIL R. WILLIAMS, M.D.

1. Huber GR: Smoking and nonsmokers: what is the issue? N Engl J Med 292:858-859, 1975
2. Hinds WC, First MW: Concentrations of nicotine and tobacco smoke in public places. N Engl J Med 292:844-845, 1975

To the Editor: The recent report by Hinds and First, of the School of Public Health of Harvard University, purports to show evidence that there may be insufficient reasons to protect nonsmokers from exposure to tobacco smoke generated by smokers.

Although their measurements may in fact be correct, and although I am inclined to believe that the danger in terms of increasing the incidence of malignant tumors and of pulmonary emphysema in nonsmokers under these circumstances is rather slight, my own experience suggests that some of the other products of smoking tend to be highly irritating and unpleasant to me personally (when there were no segregated nonsmoking sections in airplanes, my eyes watered regularly after all the smokers lit up after dinner) and to others. My observations at this medical college and others during committee meetings in poorly ventilated rooms indicate a great number of my faculty brethren to be rubbing their eyes and showing other distress as a result of the exposure to irritating components of the smoke.

It appears that Hinds and First have done a disservice to the cause of a healthy environment. Even if the danger of cancer and emphysema to the nonsmoker is minimal, there is no justification for exposure of the nonsmoking population to the irritating effects of smoke. The establishment of a nonsmoking section in vehicles of public transportation has been a most helpful step.

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APPENDIX IX

PUBLICATIONS

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PUBLICATIONS

1. LaForce, F.M., Kelly, W.J. and Huber, G.L.: Inactivation of staphylococci by alveolar macrophages with preliminary observations on the importance of alveolar lining material. American Review of Respiratory Disease 108:784-790, 1973.

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1. "Host Defenses in the Lung"
   American College of Chest Physicians
   Denver, Colorado
   October, 1972

2. "Prevention of Oxygen Toxicity in the Lung"
   American Society of Anesthesiologists
   Denver, Colorado
   October, 1972

3. "Influence of Liver Damage on the Lung"
   American College of Chest Physicians
   Denver, Colorado
   October, 1972

4. "Intrapulmonary Bacterial Inactivation Following Acute Blood Loss"
   American College of Chest Physicians
   Denver, Colorado
   October, 1972

5. "The Alveolar Macrophage as the Defender of the Lung"
   GAP Conference
   Rougemont, North Carolina
   November, 1972

6. "Basic Physiologic Changes and Antibacterial Defenses in Mice Exposed to 100 Percent Oxygen"
   American Federation for Clinical Research
   Boston, Massachusetts
   January, 1973

7. "The Effect of Experimental Stress on Pulmonary Alveolar Macrophage Function"
   American Federation for Clinical Research
   Boston, Massachusetts
   January, 1973

8. "Susceptibility to Pulmonary Infection Following Bone Trauma and Experimental Fat Embolization"
   American Federation for Clinical Research
   Boston, Massachusetts
   January, 1973

9. "Recovery of Antibacterial Defense Mechanisms in the Lung Following Partial Hepatectomy"
   American Federation for Clinical Research
   Boston, Massachusetts
   January, 1973

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10. "Recovery of Lung Injury and Host Antibacterial Defenses Following Experimental Oxygen Toxicity"
American Federation for Clinical Research
Boston, Massachusetts
January, 1973

11. "Comparative Resistance to Pulmonary Inactivation of Bacterial Species by the Lung in Oxygen Toxicity"
American Federation for Clinical Research
Boston, Massachusetts
January, 1973

12. "Adaptive Tolerance to Pulmonary Oxygen Toxicity Following Hypoxia or Intermittent Hyperpoxia"
American College of Physicians
Chicago, Illinois
April, 1973

13. "Adaptive Tolerance to Pulmonary Oxygen Toxicity Following Hypoxia or Intermittent Hyperpoxia"
American Physiological Society
Atlantic City, New Jersey
April, 1973

14. "Oxygen Recovery"
American Federation for Clinical Research
Atlantic City, New Jersey
April, 1973

15. "Aspiration Pneumonitis"
American Federation for Clinical Research
Atlantic City, New Jersey
April, 1973

16. "Dehydration and Pulmonary Host Defense Mechanisms in the Rat"
American Federation for Clinical Research
Atlantic City, New Jersey
April, 1973

17. "Intra-Alveolar Blood and Pulmonary Antibacterial Defense"
American Thoracic Society
Annual Meeting
New York, New York
May, 1973

18. "Impairment of Intrapulmonary Bacterial Inactivation Following Administration of a Commonly Used Cold Remedy"
American College of Chest Physicians
Toronto, Canada
October, 1973

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19. "The Dose-Dependent Nature of Pulmonary Oxygen Toxicity"
American College of Chest Physicians
Toronto, Canada
October, 1973

20. "Oxygen and Oxygen Toxicity"
American Heart Association
Atlantic City, New Jersey
November, 1973

21. "The Effect of Experimental Steroid Administration on the Rate of *in vitro* Phagocytosis by Alveolar Macrophages"
American Federation for Clinical Research
Boston, Massachusetts
January, 1974

22. "The Effect of Immunosuppression on the Development of Tolerance to Oxygen Toxicity"
American Federation for Clinical Research
Boston, Massachusetts
January, 1974

23. "Aspiration of Blood"
American Federation for Clinical Research
Boston, Massachusetts
January, 1974

24. "The Role of Edema in the Development of Adaptive Tolerance to Pulmonary Oxygen Toxicity"
American Federation for Clinical Research
Boston, Massachusetts
January, 1974

25. "The Effect of Experimentally Altered Thyroid Activity on Alveolar Macrophage Function"
American Federation for Clinical Research
Boston, Massachusetts
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26. "Consumption in Skid Row: A Perspective on the Focality of Active Tuberculosis in an Urban Center"
American Federation for Clinical Research
Boston, Massachusetts
January, 1974

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American Thoracic Society
Cincinnati, Ohio
May, 1974

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28. "Oxygen Toxicity and Bacterial Infection in the Lung: Impairment of Alveolar Lining Material Versus Alveolar Macrophage Bactericidal Activity"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1974

29. "Aspiration Versus Systemic Absorption as a Mechanism of Lung Injury in Experimental Kerosene Pneumonitis"
American Federation for Clinical Research
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May, 1974

30. "The Effect of Supplemental Oxygenation on the Antibacterial Host Defense Networks of the Lung"
Aerospace Medical Association
Washington, D. C.
May, 1974

31. "The Role of Immunosuppression in Oxygen Toxicity and Oxygen Tolerance"
Aspen Chest Conference
Aspen, Colorado
June, 1974

32. "Oxygen Toxicity and Bacterial Infection in the Lung"
International Academy of Chest Physicians and Surgeons
XII International Congress on Diseases of the Chest
London, England
July, 1974

33. "Impairment of Bactericidal Activity of Pulmonary Alveolar Macrophages by Exposure to Marijuana Smoke"
XXVI International Congress of Physiological Sciences
New Delhi, India
October, 1974

34. "Pulmonary Oxygen Toxicity" - Panel Presentation
American College of Chest Physicians
New Orleans, Louisiana
November, 1974

35. "Marijuana and Pulmonary Antibacterial Defenses: Depression of Alveolar Macrophage Function Following Experimental Exposure to Marijuana Smoke"
American College of Chest Physicians
New Orleans, Louisiana
November, 1974

36. "Alterations on Alveolar Lining Material as the Key Factor in Depression of Interpulmonary Antibacterial Defenses Following Stress"
American College of Chest Physicians
New Orleans, Louisiana
November, 1974

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37. "A Retrospective Analysis of Drug Therapy Used in the Management of the Acute Respiratory Distress Syndrome"
American Federation for Clinical Research
Boston, Massachusetts
January, 1975

38. "Comparative Localization of Catalase and Peroxidase Activity in Pulmonary Alveolar Macrophages"
American Federation for Clinical Research
Boston, Massachusetts
January, 1975

39. "Morphometric Ultrastructural Analysis of Alveolar Macrophages Recovered from Oxygen Toxic Animals"
American Federation for Clinical Research
Boston, Massachusetts
January, 1975

40. "The Effect of *In Vitro* Exposure to Cigar Smoke on Alveolar Macrophage Bacterial Function"
American Federation for Clinical Research
Boston, Massachusetts
January, 1975

41. "Thyroid Activity, Alveolar Macrophage Function and Pulmonary Oxygen Toxicity"
American Federation for Clinical Research
Boston, Massachusetts
January, 1975

42. "Lung Obstructive Pulmonary Disease"
Aerospace Medical Association
San Francisco, California
April, 1975

43. "Potential Pulmonary Toxicity from Drugs Used in the Management of Acute Lung Injury"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1975

44. "Stereologic Quantification of Alterations in Alveolar Macrophages Recovered from Oxygen Toxic Animals"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1975

45. "Intensification of Pulmonary Oxygen Toxicity by Prophylactic and Therapeutic Steroid Administration"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1975

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

46. "Quantitative Differences in Airway Morphology of Male and Female Rats"
American Physiological Society
San Francisco, California
October, 1975

47. "A Comparative Evaluation of Impaired Antibacterial Defenses of the Lung by Products Commonly Smoked by Man"
American College of Chest Physicians
Anaheim, California
October, 1975

48. "The Effect of Experimental Prophylactic and Therapeutic Steroid Administration on the Course of Oxygen Toxicity"
American College of Chest Physicians
Anaheim, California
October, 1975

49. "Recovery of Alveolar Macrophages from Lung Washings. A Stereologic Evaluation"
American College of Chest Physicians
Anaheim, California
October, 1975

50. "Quantitative Differences in Airway Morphology Secondary to Sexual Function"
American College of Chest Physicians
Anaheim, California
October, 1975

51. "Impairment of Antibacterial Defenses of the Lung by Marijuana Smoke"
Internal Medicine Post-Graduate Course
Vail, Colorado
January, 1976

52. "The Role of Diabetes Mellitus in Pulmonary Infection: An Experimental Model"
American Federation of Clinical Research
Boston, Massachusetts
January, 1976

53. "The Combined Effects of Tobacco and Alcohol on the Host Defense System of the Lung"
American Federation of Clinical Research
Boston, Massachusetts
January, 1976

54. "Which Steroid to Use? Variability of Impairment of Host Intrapulmonary Antibacterial Defenses as a Function of Steroid Turnover"
American Federation of Clinical Research
Boston, Massachusetts
January, 1976

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55. "Comparative Evaluation of Synthetic Smoking Materials and Tobacco Cigarette Blends on Alveolar Macrophage Bactericidal Activity"
American College of Physicians
Philadelphia, Pennsylvania
April, 1976

56. "Comparative Stereology of Alveolar Macrophages from Chronically Smoked Rats"
Federation of American Societies for Experimental Biology
Anaheim, California
April, 1976

57. "Models of Lung Injury"
International Chest Conference
Tel-Aviv, Israel
April, 1976

58. "The Antibacterial Defenses of the Lung"
International Chest Conference
Tel-Aviv, Israel
April, 1976

59. "The Alveolar Macrophage, Tobacco Smoking, and the Lung"
International Chest Conference
Tel-Aviv, Israel
April, 1976

60. "Differential Response of Male and Female Airway Epithelium to Chronic Tobacco Smoke Inhalation"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1976

61. "The Effect of Tobacco Smoke on the Metabolic Functions of Alveolar Macrophages"
American Society of Clinical Investigation
Atlantic City, New Jersey
May, 1976

62. "Mechanisms of Impairment of Pulmonary Antibacterial Defenses Induced by Stress"
American Federation for Clinical Research
Atlantic City, New Jersey
May, 1976

63. "The Role of Basic Metabolic Patterns in Impaired Intrapulmonary Antibacterial Defenses Following Exposure to 100 Percent Oxygen"
Aerospace Medical Association
Bel Harbour, Florida
May, 1976

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64. "The Combined Effects of Alcohol and Marijuana or Tobacco on the Antibacterial Defenses of the Lung"
American Thoracic Society
New Orleans, Louisiana
May, 1976

65. "Temporal Relationships of Exposure to Tobacco Smoke on the Impairment of Pulmonary Antibacterial Defenses"
American Thoracic Society
New Orleans, Louisiana
May, 1976

66. "The Biological Effect of Tobacco Cigarette Smoke on the Host Defense System of the Lung"
American Physiological Society
Philadelphia, Pennsylvania
August, 1976

67. "The Lung and the Environment"
Wolowelski Memorial Lecture
Haifa, Israel
October, 1976

68. "Acute Lung Injury: Models for Evaluating Pulmonary Host Defenses"
Wolowelski Memorial Lecture
Jerusalem, Israel
October, 1976

69. "Steroid and Pulmonary Antibacterial Defenses"
Wolowelski Memorial Lecture
Tel-Aviv, Israel
October, 1976

70. "Oxygen Therapy and Oxygen Toxicity"
Wolowelski Memorial Lecture
Beersheva, Israel
October, 1976

71. "Tobacco Smoke, Alveolar Macrophage, and Lung Disease"
Wolowelski Memorial Lecture
Haifa, Israel
October, 1976

72. "The Mechanisms of Impairment of Alveolar Macrophage Defenses by Acute Exposure to Tobacco Smoke"
American College of Chest Physicians
42nd Annual Scientific Assembly
Atlanta, Georgia
October, 1976

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

73. "Does Tobacco Smoke Impair Alveolar Macrophage Function?"
American College of Chest Physicians
Atlanta, Georgia
October, 1976

74. "Lipid Deposition in Pulmonary Alveolar Macrophages After Cigarette Smoke Exposures: A Morphometric Study"
American College of Chest Physicians
Atlanta, Georgia
October, 1976

75. "A Comparative Evaluation of Synthetic Smoking Materials and Natural Tobacco Smoke on the Antibacterial Defenses of the Lung"
American College of Chest Physicians
42nd Annual Scientific Assembly
Atlanta, Georgia
October, 1976

76. "The Effect of Tobacco Smoke on Enzymes Relevant to Oxygen Metabolism in Pulmonary Alveolar Macrophages"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

77. "The Effect of Acute and Chronic Experimental Tobacco Smoke Inhalation on Rat Alveolar Macrophage Bactericidal Function"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

78. "Lipid Accumulation and Volume Changes in Pulmonary Macrophages After Prolonged Tobacco Exposure"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

79. "Quantitative Morphologic Sex Differences of Tracheal Gland Secretion and Hypertrophy in Response to Chronic Tobacco Smoke Inhalation"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

80. "Characterization of Individual Inhalation Profiles During Human Tobacco Cigarette Smoking"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

81. "The Effect of Iron Oxide Inhalation on the Antibacterial Defense System of the Lung"
American Federation for Clinical Research
Eastern Section
Boston, Massachusetts
January, 1977

1003535706

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

82. "Characteristics of Pulmonary Surfactant Following Inhalation of "Tobacco Smoke"
American Physiological Society
Chicago, Illinois
April, 1977

83. "Comparative Study of Acute Effects of Albuterol and Isoproterenol Sulphate Aerosols in Bronchial Asthma"
Massachusetts Thoracic Society
Cape Cod, Massachusetts
April, 1977

84. "Clearance of Cigarette Smoke Gas Phase Alveolar Macrophage Cytotoxins in a Model Airway System"
American Federation for Clinical Research
Washington, D.C.
May, 1977

85. "The Effect of Tobacco Smoke on Oxidative Metabolism and Enzymes of Rat Pulmonary Alveolar Macrophage (PAM)"
American Federation for Clinical Research
Washington, D.C.
May, 1977

86. "Characterization of Lipid Inclusions in Alveolar Macrophages after Tobacco Smoke Exposure"
American College of Chest Physicians
Las Vegas, Nevada
November, 1977

87. "Albuterol and Isoproterenol Aerosols: Comparative Evaluation of Cardiopulmonary Effects in Brochial Asthma"
American College of Chest Physicians
Las Vegas, Nevada
November, 1977

88. "Changes in Composition of Gas Phase Cigarette Smoke After Passage Over Wetted Surfaces"
31st Tobacco Chemist Research Conference
Louisville, Kentucky
October, 1977

89. "Alterations in Lung Parenchyma Following Experimental Chronic Inhalation of Tobacco Smoke"
American College of Chest Physicians
Las Vegas, Nevada
November, 1977

90. "Stereologic Estimation of Volume and Surface Area of Three-Dimensional Bodies Using Modified Random Planar Sections"
Biometric Society
Lexington, Kentucky
March, 1978

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

91. "Effects of Synthetic Tobacco Substitute Cigarette Smoke on Alveolar Macrophage Bactericidal Activity"
American Thoracic Society
Boston, Massachusetts
May, 1978

92. "The Tobacco and Health Controversy"
State-of-the-Art Symposium
American Thoracic Society
Boston, Massachusetts
May, 1978

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APPENDIX X

A. Lorillard Smoking Machine

B - D. Reprints Relatated to the Lorillard Smoke Delivery System

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SMOKE INHALATION APPARATUS

Although several laboratories have published information on the response of the lung following the experimental exposure of animals to tobacco smoke, most of these results are controversial and subject to considerable criticism. The primary reason that experimental smoke inhalation studies have been so unsuccessful in the past is that there have been no smoking machines that could create a stable aerosol of either tobacco or marijuana smoke, comparable to that created by man when he smokes these products, that could be delivered to the lungs of experimental animals. It is our evaluation that all existing commercial machines now used fail in this crucial requirement. To solve this problem, we have built a total of four Lorillard smoking machines for our laboratory. This machine was initially developed primarily by the tobacco industry.

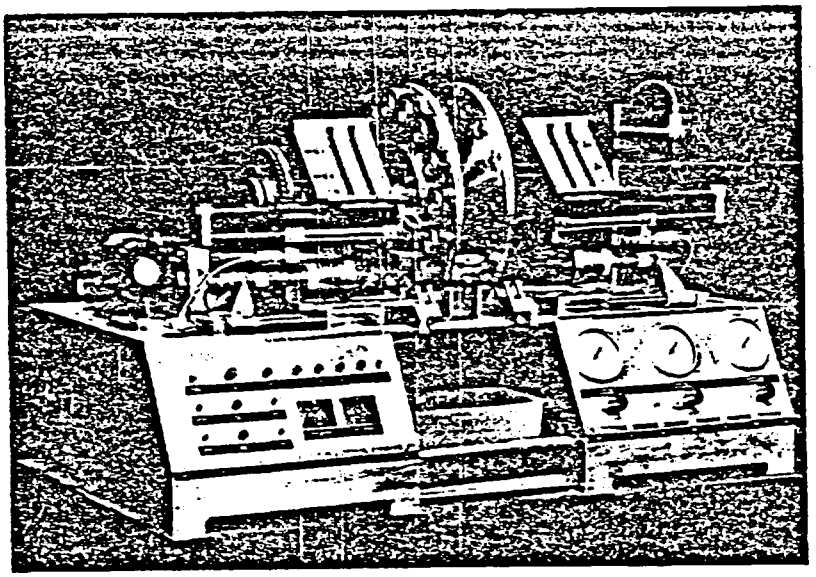

Figure X-1: The Lorillard smoking machine, capable of generating a stable cigarette smoke aerosol for delivery to the lungs of experimental animals.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

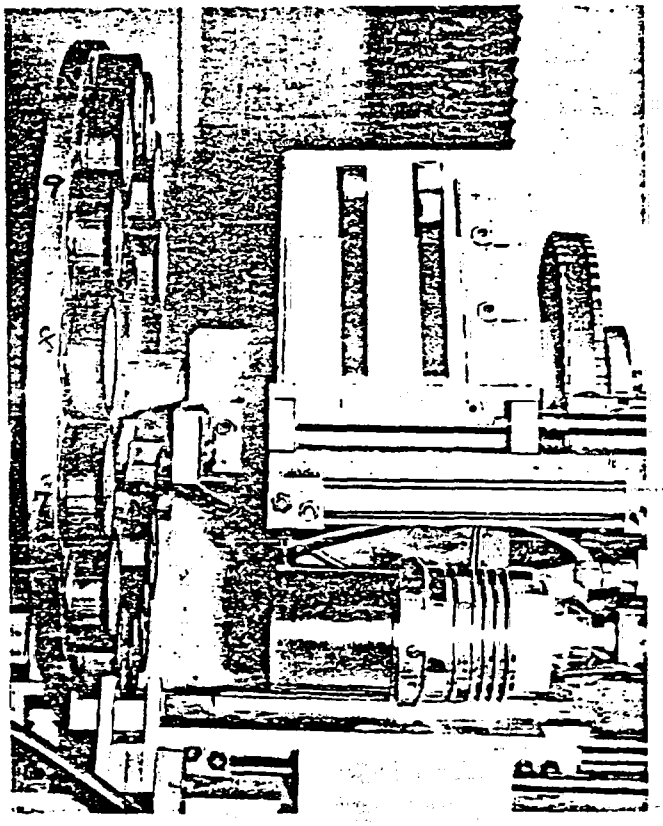

Figure X-2: A view of the loading cassette of the smoking machine. There are 30 portals for cigarettes, with 15 on each of the two rotating wheels. Cigarettes are automatically loaded and ejected after a predetermined number of puffs, usually 10. All cigarettes are conditioned with standardized humidity and temperature prior to use and burned, for the most part, to a consistant butt length.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

One such smoking machine is shown in Figure X-1. These are very complex pieces of equipment and now cost over $30,000 each to construct. They have the capacity to expose approximately 150-450 experimental animals to various concentrations of tobacco or marijuana smoke per hour. Once operational, they appear, in our experience, to be able to run for literally months, with a minimum of maintenance or breakdown.

In the development of a smoking machine for the delivery of fresh smoke at ambient pressures to animal exposure systems, several design parameters are dictated if a wide range of exposure conditions are to be obtainable. Reverse smoking (the creation of a pressure around the lighted end to generate smoke exiting through the delivery system) is necessary to fulfill the requirement for fresh smoke at ambient pressure. A 30 port design resulted from the standard smoking conditions of a 35 ml puff with a two-second time duration once per minute. The 30 ports are logically broken into two groups because of the positioning, dwell, and reaction times associated with this system. A rotary positioning arrangement was preferred, since the smoking cycle is repetitious and the time cycle is fixed. Further, the cigarettes and delivery system should rotate in preference to the reverse smoking chamber(s), since this avoids rotary valves or cumbersome tubing arrangements.

Reverse smoking entails several difficulties which are not encountered where smoke is generated by pulling a vacuum on the cigarette. It is more diffucult to ensure the delivery of the correct volume of smoke. An accurate flow control system is mandatory and this will produce a nearly square puff profile, but it is difficult to decide upon the proper flow rate of the input air for puff generation. Not all cigarettes have the same pressure drop, and this will increase to a variable degree as a cigarette is lit and puffed, although all may have the same pressure drop initially. Pressurized air in the chamber is exhausted at the end of each puff, and the quantity is dependent upon the size of the chamber and the magnitude of the pressure drop. The combustion of the cigarette adds to the total volume generated during each puff and may vary from cigarette to cigarette. These experimental difficulties may be compensated for by careful design. Although reasonable estimates can be made for all factors, careful calibration with test cigarettes is needed, and this is done in our unit on a regular basis.

Further design criteria are a natural result of the foregoing requirements. There is, in our machine for example, the need for a smooth, stepwise rotary motion to position the cigarettes. The geneva movement provided an ideal solution, since it is very smooth and additionally offers dependability, low wear, accuracy of positioning and timing, and can be made rugged and maintenance free.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

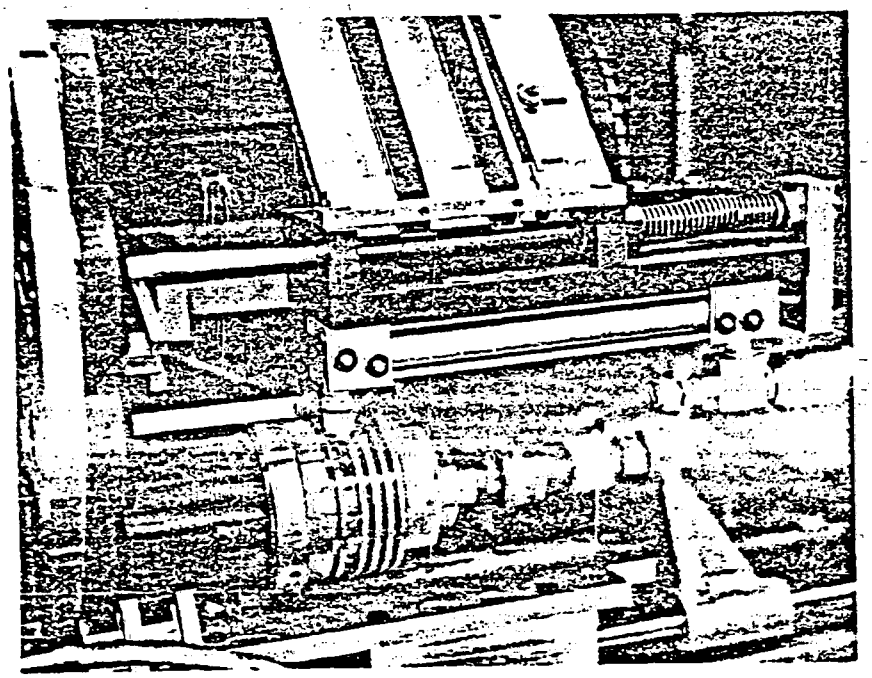

Figure X-3: Shown in this photograph is a view of the cigarette being loaded into a portal. This must be done under slight pressure. Tobacco cigarettes, that are tightly packed, immediately reform their original shape, as shown in the lower of the two cigarettes seen above.

In our machine the cigarettes are loaded into a cassette, as shown in Figure X-2 and automatically supplied to the cigarette holders as shown in Figure X-2 and Figure X-3. Once loaded, the puff chamber closes on the rubber cams and a standard amount of tobacco smoke is generated, created as a stable aerosol, which remains stable until delivery to the lungs of the experimental animals. Shown in Figure X-4 is the puff-chamber approaching the loaded and burning cigarette, and shown in Figure X-5 is the puff-chamber tightly closed around the rubber cam and the cigarette, delivering its puff that creates the stable exposure aerosol. The smoke generated is then passed through a dispersion system and a series of tubes. These are special conductors that do not allow the aerosol to precipitate on their walls in any significant manner and permit delivery of the generated smoke to the lungs of the animals in less than 0.2 seconds.

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Air was chosen as the motive force for linear motion, since a rather long stroke was necessary to position a chamber over the cigarette, and for positive action and speed of response the stroke had to be powered in two directions. Since the machine had to be divided into two smoke-generating sections the shuttling action needed to couple them to the exposure system was easily accomplished.

A single timing source for all functions was desired, since this precludes any loss of synchronization. In conjunction with this requirement was the need for an efficient system of interlocks to prevent damage, and to ensure that the system, if not in proper operating condition, will not operate at all.

All timing originates from a synchronous motor. This motor serves a dual purpose in that it is coupled through a gearing mechanism to a four-position geneva movement and to the shaft of a sequence programmer. The motion of the geneva movement is transmitted through a notched timing belt to index the cigarette holders.

Ten pounds of pilot air pressure is supplied by a regulator to the valves of the sequence program. The cams on this programmer actuate the four control valves which power actuators on the four-way valves, which in turn control the motion of air cylinders on the puff chamber and the shuttle valve. An additional regulator supplies the 45 pound control air which will power both the puff chamber air cylinders and the shuttle valve. Should this air system fall below 40 psi the pressure switch would interrupt the operation of the machine.

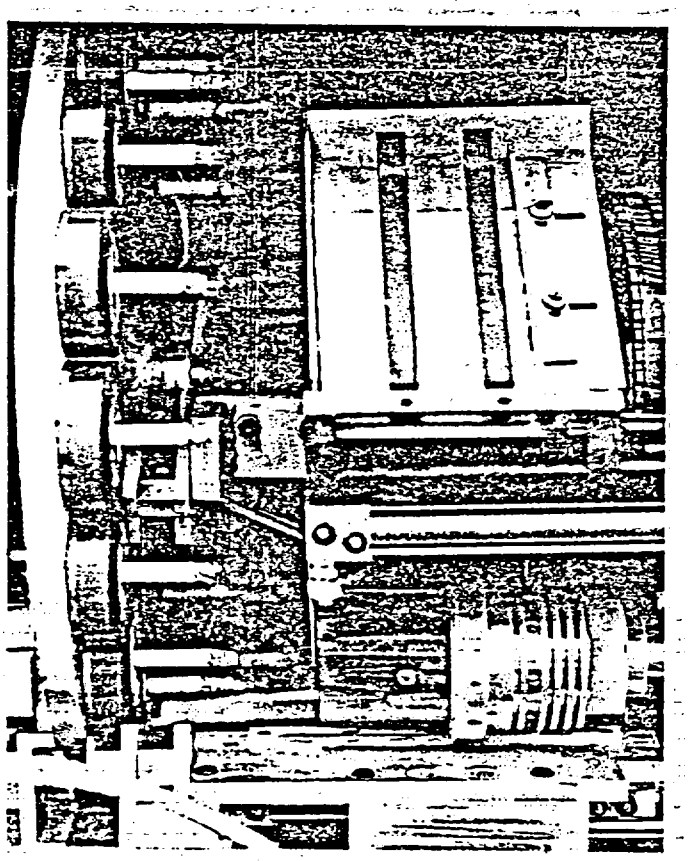

Figure X-4: Cigarettes are in place and burning in each portal. The only smoke generated under these conditions is the side-stream component. The puff-generating chamber is withdrawn in this position, allowing an automated programmed rotation of the cigarettes between smoking.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

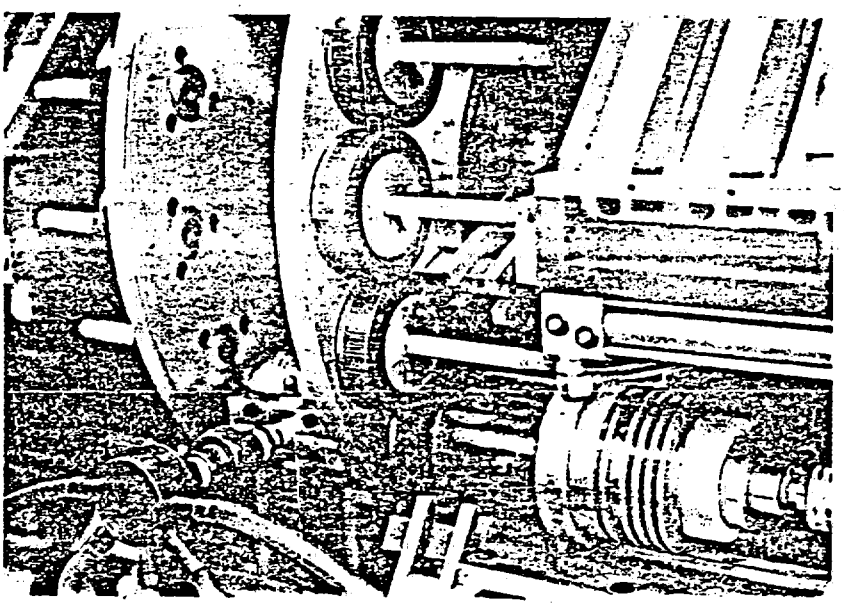

Figure X-5: The puff-chamber is closed on the rubber cam and generating 35 milliliters of fresh cigarette smoke. The puff volume and generation time can be programmed to any desired criteria.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

The cigarette smoke, once generated, is rapidly distributed to the conducting tubes and exposure chambers, as shown in Figure X-6 and Figure X-7. Although the delivery system could be expanded, we are comfortable with our current capacity to expose 50 rats at one time in each smoking machine. For our pigeon exposures, we have used a shuttle-valve and a full-loading complement of cigarettes to expose three, rather than one, carousels during each sequence.

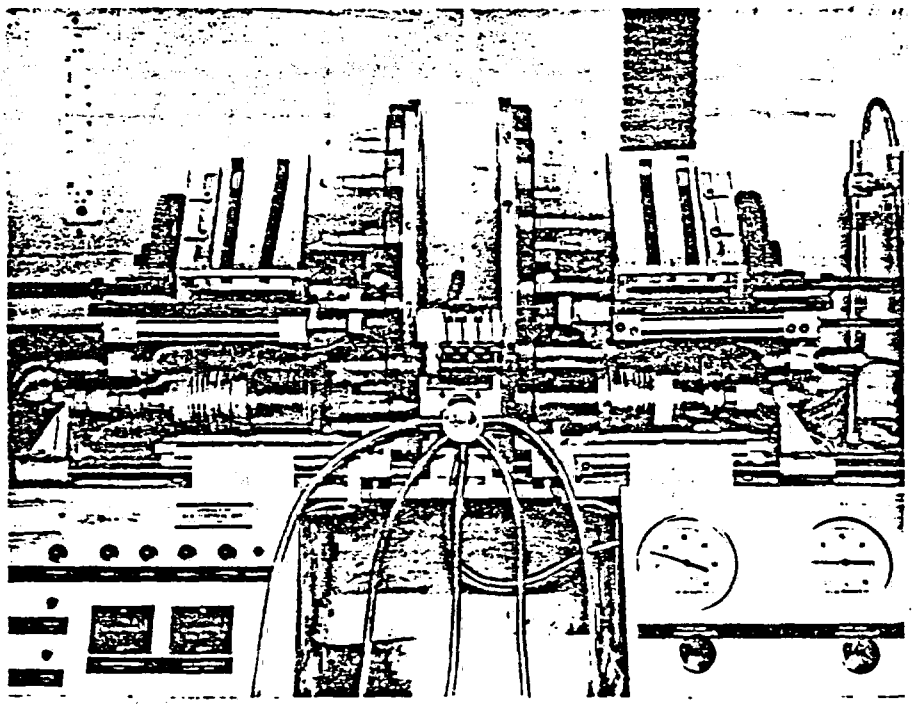

Figure X-6: Frontal view of the smoking machine in operation, with the five delivery tubes shown anteriorly. The puff-chamber on the right is generating fresh smoke and the one on the left is in an intermediate position.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

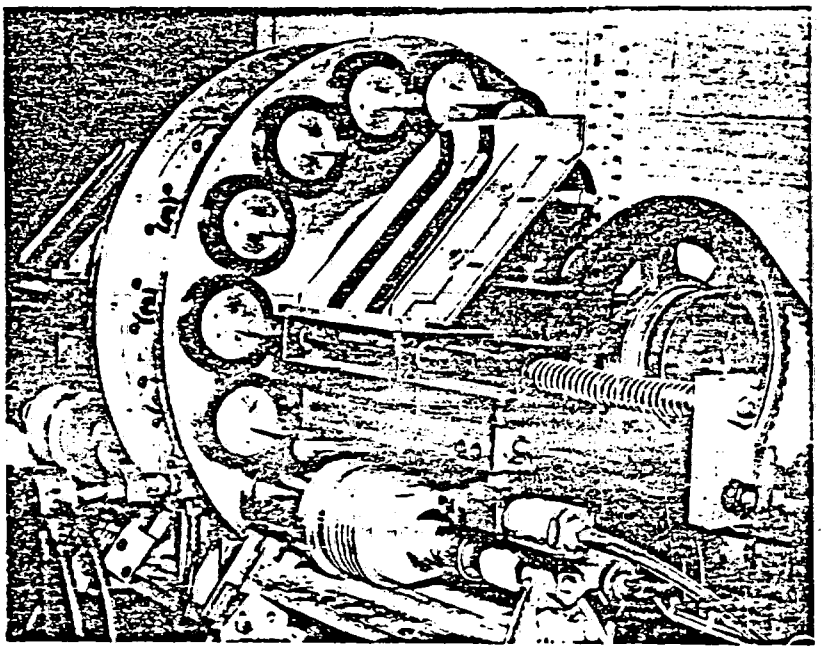

Figure X-7: An oblique view of the smoking machine with the dispersion conducting system.

Shown in Figure X-8 is the carousel used to hold the exposed rats, with the delivery or conducting tubes at the top and the exhaust system at the bottom. The flow of the aerosol is rapid and does not allow agglomeration or condensation of the fresh smoke aerosol nuclei in any significant degree. As can be seen, fifty rats can be exposed simultaneously in this system. The animals are held in small containers, shown in greater detail in Figure X-9 and Figure X-10. These containers involve an interlocking system for efficient and rapid loading and placement in the chamber. Once in place, the animals are relatively comfortable and inhale the smoke product as it passes through the exposure system. A very significant portion of our efforts in the funded period to date has been spent perfecting this smoke-exposure system and reducing the level of stress in the exposed animals to an absolute minimum.

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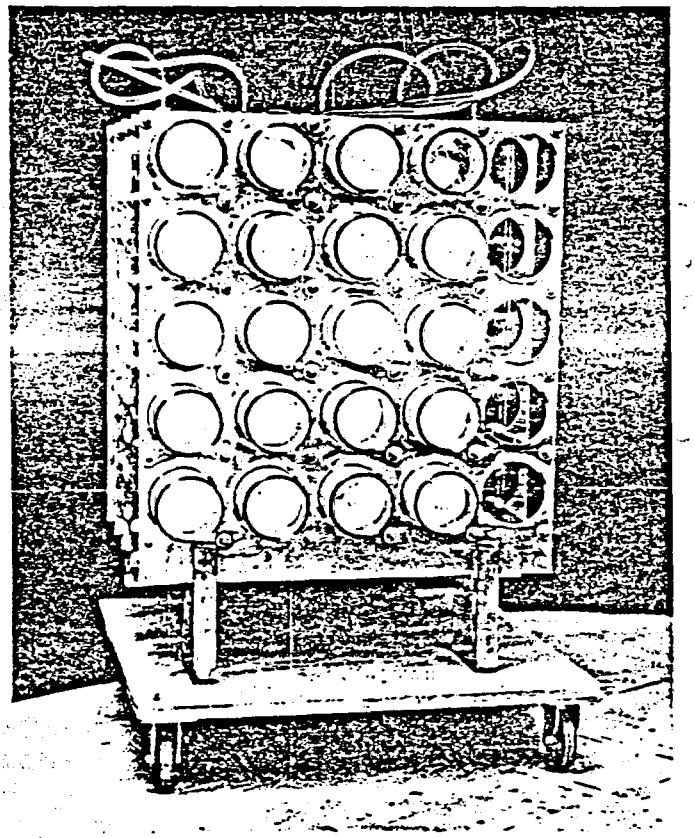
Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000



the delivery or conducting tubes at the top and the exhaust system at the

Figure X-8: The smoke-exposure carousel. Fifty rats can be exposed at one time. Each carousel is mounted on wheels for mobility and easy transport of animals from their housing to the exposure room and the smoking machines.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

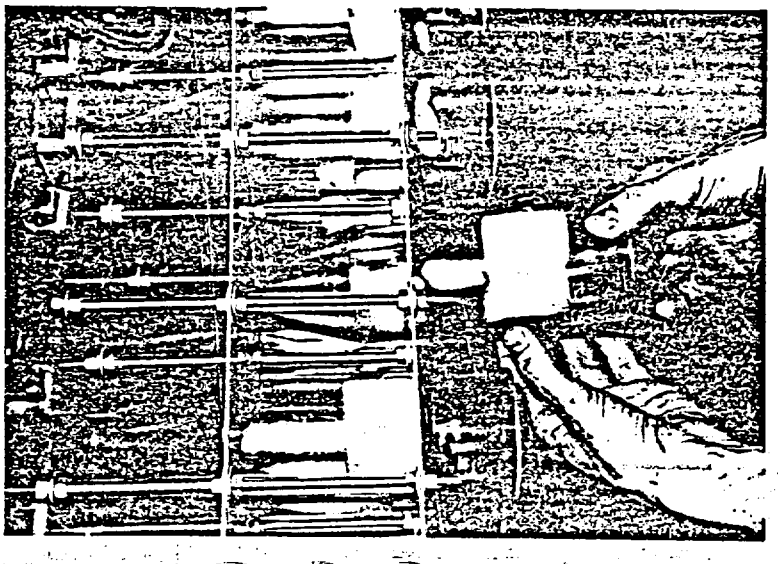

Figure X-9: The animal-holding chambers are transparent and can be easily removed from and placed in the exposure carousel. Animals are comfortably held in place by the sponge-rubber plug in the rear of the chamber.

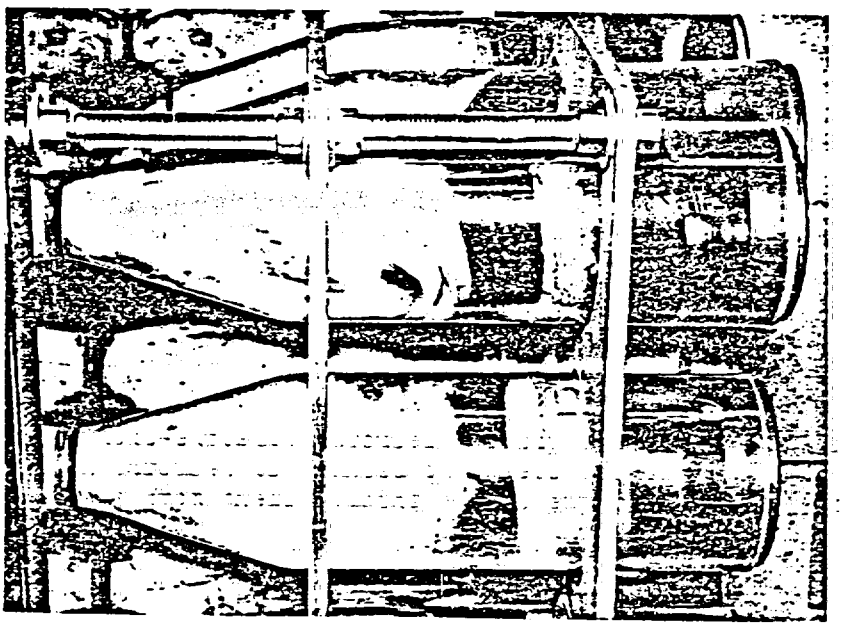

Figure X-10: A rat in place during exposure to smoke. This delivery system has the versatility to expose any sized animal, from the smallest rodent to an animal the size of a horse or larger, to the same stable aerosol of fresh smoke.

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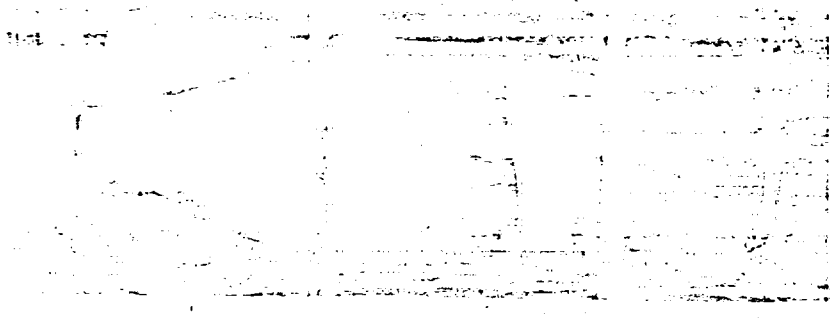
Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

Our pigeons are exposed with a different system. We believe it is essential for the success of the experimental inhalation, that the pigeons be immobilized during smoke exposures to prevent them from putting their head under a wing (thereby screening out much of the particulate phase). We also believe that only the beak and nares should be exposed to the fresh smoke to avoid soiling the pigeon plumage with tar. Otherwise, the birds will injest substantial amounts of smoke products when they preen their feathers. These factors could be minimized with the hood and glottal cannula system, but as stated above we believe intubation to be impratical for long term studies of large number of pigeons, not only because of high man-power requirements, but, more importantly, because we believe repeated intubation would result in excessive premature losses of birds from physical injuries over the period of the proposed study. We are, therefore, developing a new method of exposing pigeons to tobacco smoke that is very gently and which will present smoke solely to the birds respiratory systems. Following closely the recommendations of Professor B. F. Skinner, we prepare the pigeons for their daily smoke exposures by immobilizing them in a closely-fitted cuff that could potentially be left around the birds for the duration of the total daily smoking period (6-8 hours). Professor Skinner, who has had extensive experience with these methods, has assured us that continuous confinement by this technique for the periods noted produces no discernable physical or physiological harm to the birds or any significant psychological stress. This system of immobilization could reduce in a major way the handling of the birds, thus reducing the cost of exposure and lessening the potential for accidental injury.



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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

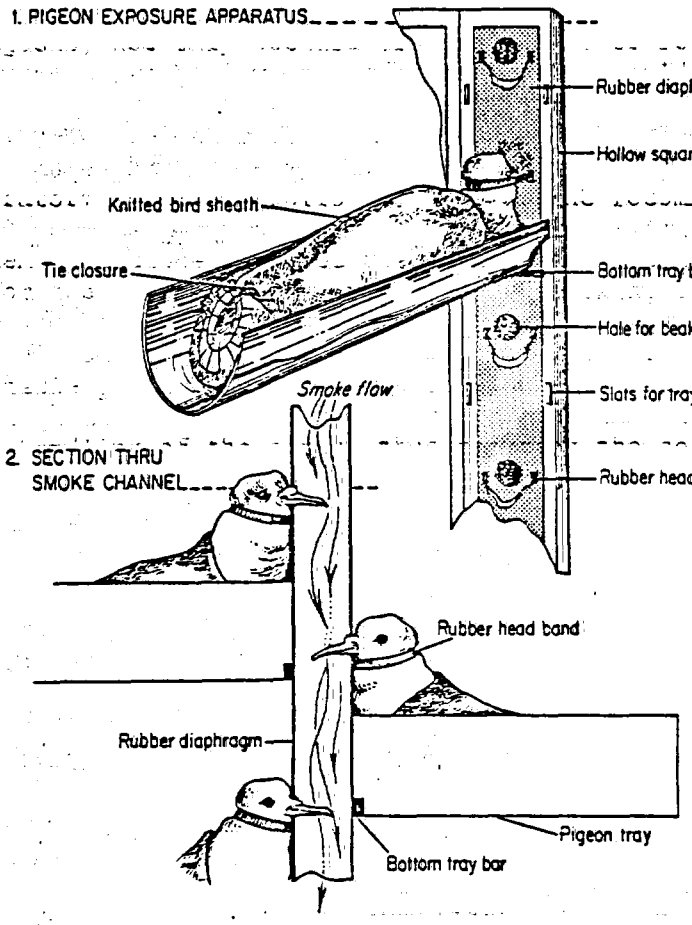

Figure X-11: Diagramatic illustration of the proposed method of immobilizing pigeons and exposing only their respiratory system, by noninvasive techniques, to cigarette smoking products.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

FRONT VIEW OF 60-PIGEON EXPOSURE RACK

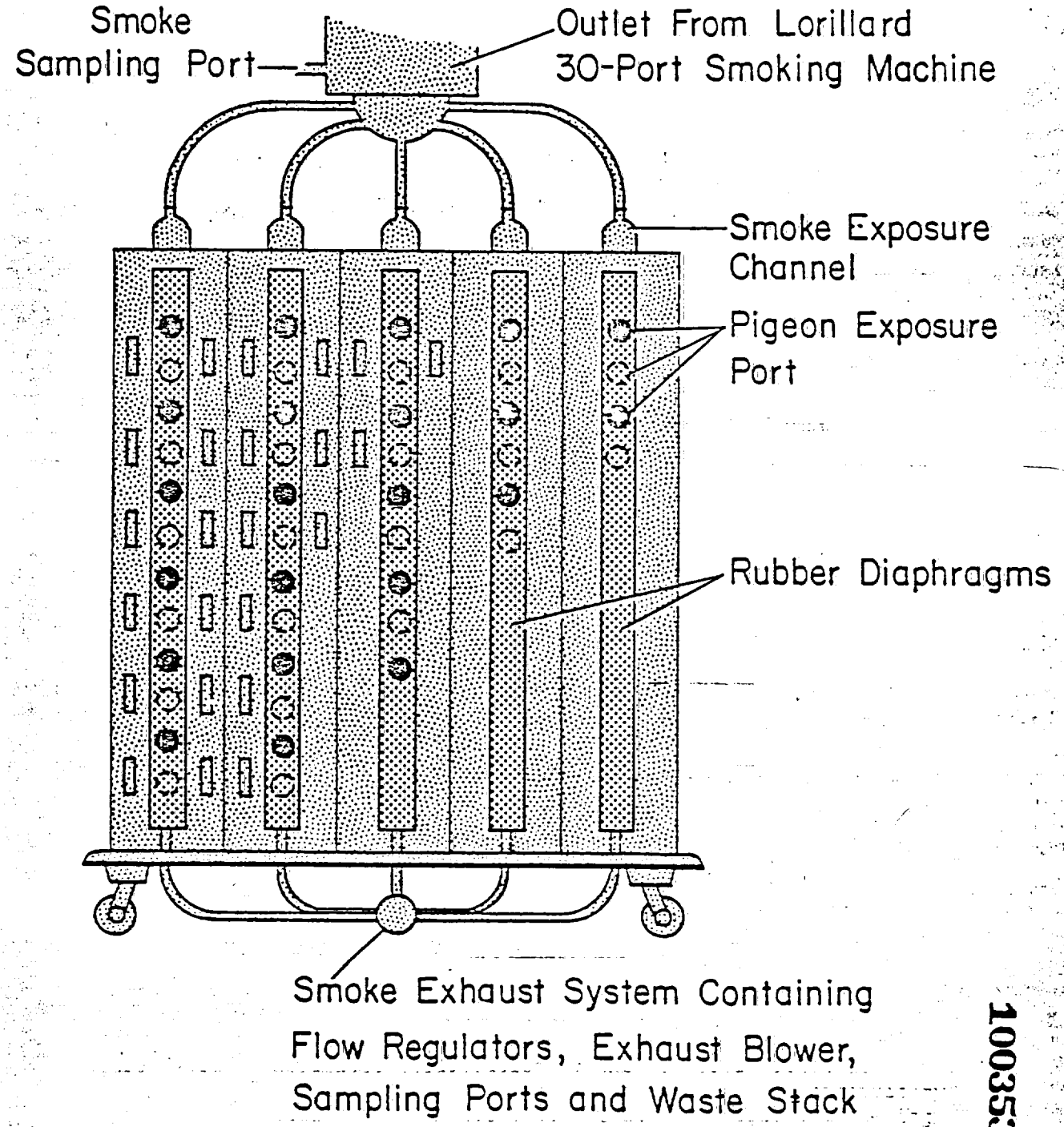

Figure X-12: Schematic diagram of the pigeon exposure rack.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

To expose only the beak and nares of the birds to tobacco smoke, we constructed an exposure apparatus containing a rubber diaphram with holes of appropriate size and locations through which the bird's beak, up to and including the nares, can be inserted to form a gas-tight seal. This is illustrated in Figure X-11 and Figure X-12. Tobacco smoke suitably diluted, or spiked with carbon monoxide, passes through a channel on the side of the flexible diaphram in which the beak and nares are located, while the remainder of the bird remains in clean laboratory air. A helmet attached to the diaphram is gently slipped over the bird's head to prevent it from withdrawing its beak from the smoking portal. Because the diaphram is soft and flexible, movements of the bird's head while exposed to smoke will neither produce injury nor break the firm seal between the smoke channels, on one side, and the laboratory atmosphere on the other.

To equate exposure levels (smoke delivered to the whole animals) for both our pigeon and rat experiments with dosimetry (actual amount of smoke inhaled), we have perfected a method of lacing all units with a nonradioactive chlorinated hydrocarbon, decachlorobiphenyl (DCBP). The lacing machine shown in Figure X-13 is used to evenly deposit tracer into a single cigarette. With this machine it is possible for one operator to lace 85 cigarettes per day with an accuracy, characterized by a relative standard deviation, of 1%.

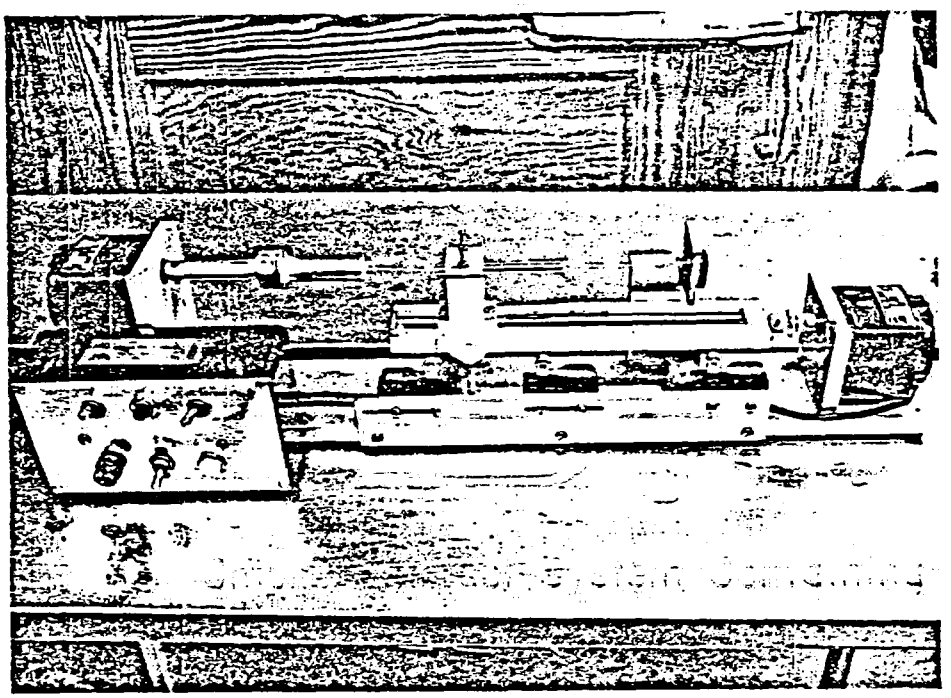

Figure X-13: Lacing machine.

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Figure X-14 shows and enlargement of the lacing machine cigarette holder. The cigarettes are manually placed in this holder. When the machine is switched on, the holder rotates the cigarettes slowly allowing for even deposition of tracer. Figure X-15 shows an enlargement of the syringe mechanisms of the lacing machine. Due to modifications of the machine the syringe is filled manually with DCBP tracer using chloroform as a solvent. The syringe assembly is then switched on to drive the 100 µl syringe into the cigarette. When the syringe needle reaches the end of the cigarette it is stopped automatically. At this point a butt plate is placed behind the plunger of the syringe and the syringe withdrawn, automatically depositing equal amounts of tracer throughout the full lingth of the cigarette.

By using this system, we can deliver "laced" smoke to the animals. Total "tar" in the delivery stream is quantified by the gravimetric methods and cross-calibrated with tracer content. The total amount of tracer in the lungs of each animal is quantified by chromatographic analysis. Then, by back calculating to the tar-lacer ratio in the smoke delivered, the exact amount of tar delivered to the lungs of animals can be accurately determined. By using these techniques, and by also simultaneously meansuring CO in the gas phase of the delivered smoke and HbCO in each animal, we have an accurate assessment of both gas phase and total-particulate delivery of smoke to each individual animal. From these measurements precise correlations between biologic effects and true dosimetry can be determined.

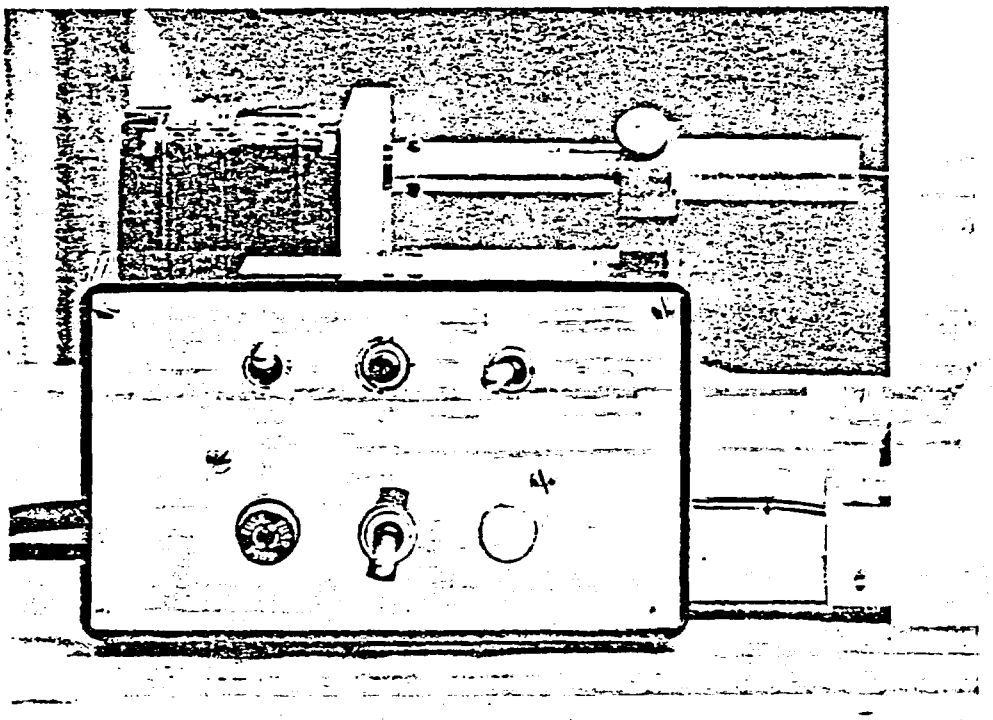

Figure X-14: Lacing machine cigarette holder.

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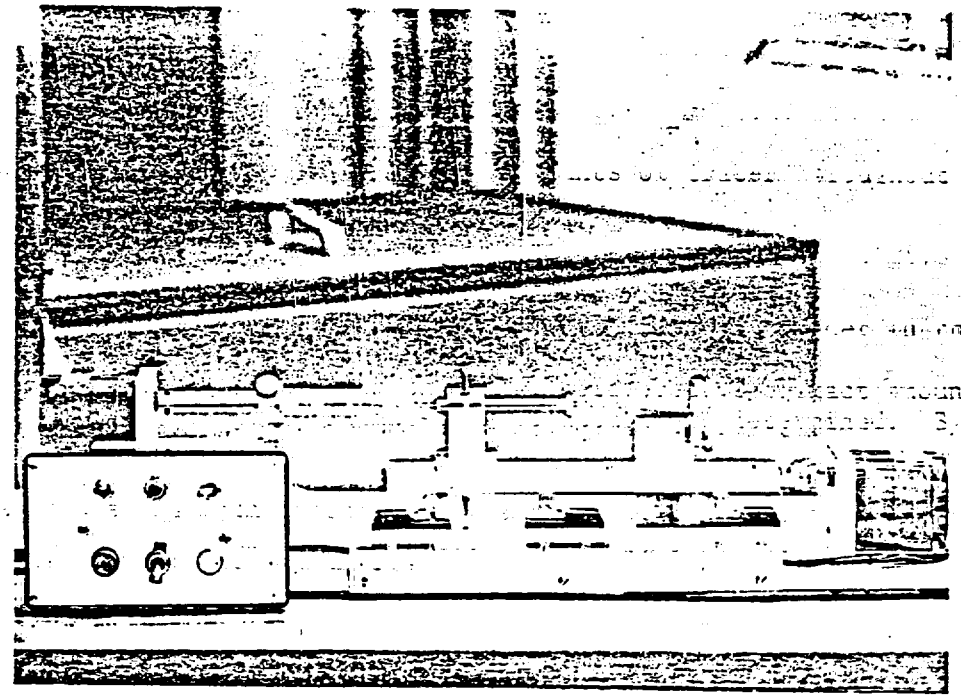

Figure X-15: Lacing machine syringe mechanism.

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A Thirty-Port Smoking Machine for Continuous Smoke Generation*

by F. J. Schultz and J. R. Wagner
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INTRODUCTION

During recent years, there has been a steadily growing interest among biomedical research scientists in studying the effects of inhaled cigarette smoke on small animals. One of the serious handicaps faced in these studies has been the lack of availability of apparatus necessary to perform inhalation experiments involving large numbers of animals. A major item required in any such experiment is a machine capable of producing cigarette smoke in a well defined and consistent manner. In an effort to alleviate this problem, the *Council for Tobacco Research U.S.A.* (CTR) undertook a program to solicit smoking machine designs from many sources and to evaluate the performance of the machines submitted for testing.

It became apparent during these tests that none of the machines then known to exist would meet the criteria considered necessary for the intended application. Some of the more important criteria were:

1. The machine should smoke cigarettes according to the standard analytical smoking parameters of a puff volume of 35 cm^3 taken during a time of 2 seconds duration once each minute.
2. The smoke should be delivered to the test animals with a minimum delay in order to prevent chemical or physical property changes due to aging.
3. A reliable means for providing a known amount of air dilution should be provided.
4. Methods of conveniently monitoring the performance of the machine with respect to the smoking parameters and convenient methods for collecting smoke samples for analysis must be incorporated in the design.
5. The design should provide the capability of exposing large numbers of animals simultaneously.

One direct result of this CTR program was the development of the Walton-Morrissey Smoking Machine (1, 2). This machine utilizes the reverse puffing technique and can puff one, two or three cigarettes simultaneously into a chamber which will accommodate the exposure of 12 mice or hamsters at one time.

We were in the process of designing a smoking machine at the time that the CTR evaluation program was going on. We were therefore in the fortunate position of being able to gain considerable insight into the various problems and successes encountered in those tests and to take them into account in the design of our machine. Since there was, and apparently still is, little agreement among researchers on the best way to restrain animals during inhalation experiments, we decided to devote our principal efforts to the design of an apparatus for the production of smoke under closely controlled and well defined conditions, and only secondarily to animal holder systems.

Two general methods of puffing a cigarette are possible. The most common is to draw smoke from the cigarette by application of a vacuum to the butt end. The other, known as reverse smoking, is to force air through the lighted cigarette by applying an elevated pressure to the burning end. The delivery of smoke to animals using the first method would require collecting the smoke drawn from the cigarette and then transferring it to the animal exposure device or placing the animals under reduced pressure during puffing. The disadvantages of this system with respect to the time lapse involved and the handling and transfer of a labile aerosol are obvious. We chose reverse smoking as the preferable method of smoke generation because the smoke could be routed directly to the animal holder from the cigarette butt with a minimum of manipulation and lost time.

* U.S. Patent No. 3, 732, 874.

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Figure 1. Overall view of the smoking machine.

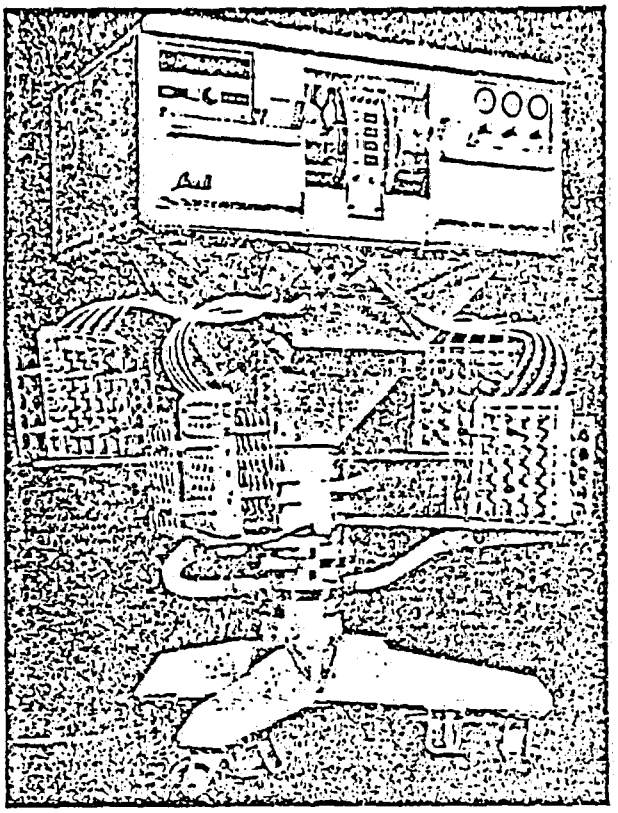
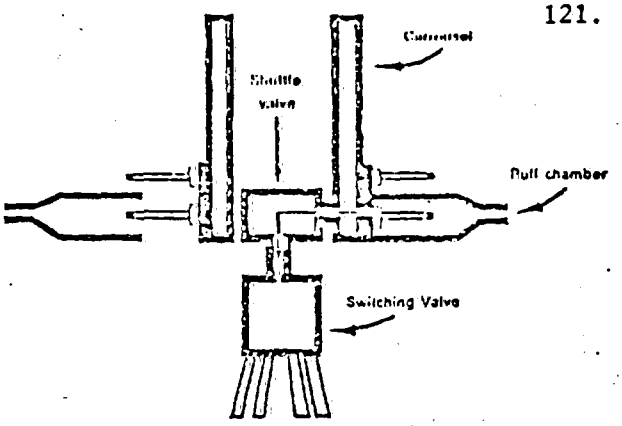


Figure 2 Schematic of smoke generation system.



APPARATUS

Having made this basic commitment to the method of smoking, we designed the apparatus pictured in Figure 1 and shown diagrammatically in Figure 2. The operational sequence can best be followed by referring to Figure 2. The puff chamber to the right moves over the cigarette and seals against the cigarette holder. Simultaneously, a calibrated amount of air is admitted to the puff chamber and the central shuttle valve moves to the right to make a seal against the cigarette holder at the butt of the cigarette. The resulting puff profile (Fig. 3), as measured in the puff chamber, is sharply squared on the leading and trailing edges, and is modified during the course of the puff by the burning characteristics of the individual cigarette. During the two-second period while air is being forced through the cigarette and the smoke is being routed out through the shuttle valve channel, the left hand cigarette holder carrousel is being rotated to align the second cigarette with the shuttle valve and the left puff chamber. At the end of a two-second puff of the first cigarette, the left puff chamber moves in and seals over the second cigarette, the shuttle valve moves left and seals over the butt opening, puff air pressure is supplied, and the right puff chamber retracts. During the two-second puff on the second cigarette, the right carrousel moves cigarette number three into position and at the end of the puff on cigarette number two the above cycle is repeated.

Each carrousel holds 15 cigarettes which are puffed alternately for two seconds each, providing one puff per minute on each cigarette, thus resulting in a constant stream of smoke being emitted from the shuttle valve outlet.

The details of how these functions are made to occur in the proper sequence and at the proper time are beyond the scope of this paper but they are programmed by cam operated switches and air valves in an earlier model and by digital electronics in the model reported here.

The machine is equipped with automatic cigarette loading, lighting, and butt ejecting mechanisms. The automatic lighter (located within the puff chamber) lights each cigarette during the first puff cycle and then turns off until the next group is loaded. The cigarette butts are ejected after a preset number of puffs have been taken on each cigarette.

Since the two-second puff time is preset, the only variables that need to be calibrated to conform to the standard smoking procedures are the puff air volume and the diluting air flow. The 35 ml puff generated is the result of two components; the gases generated by the burning cigarette and the air forced through the cigarette. It is therefore necessary to calibrate this puff on the basis of output smoke rather than input air. This is done by the following procedure.

The machine is loaded with thirty cigarettes and the smoking cycle is begun. The continuous stream of diluted smoke from the machine is delivered into a

Figure 3. Puff profile.

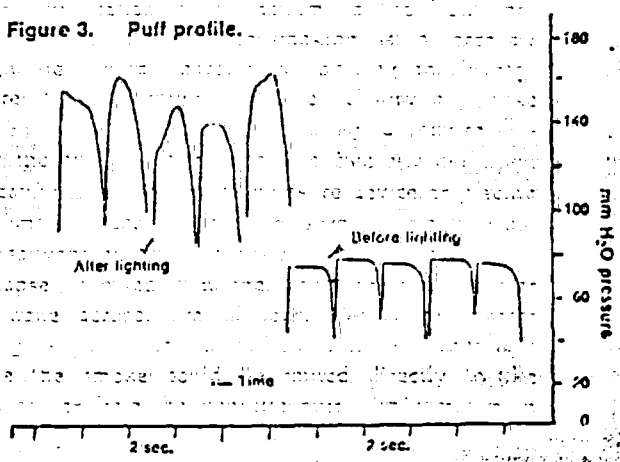


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Figure 4. Right hand panel.

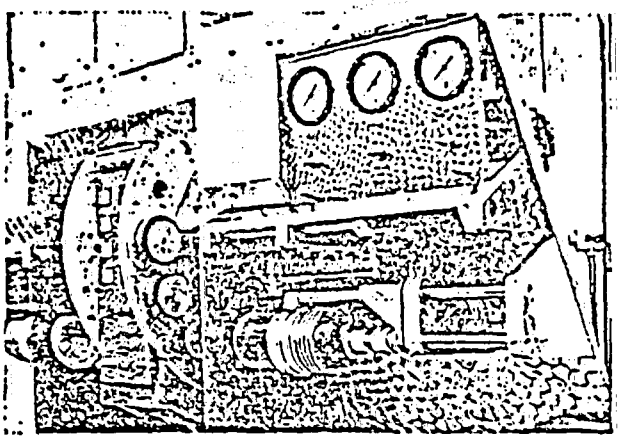
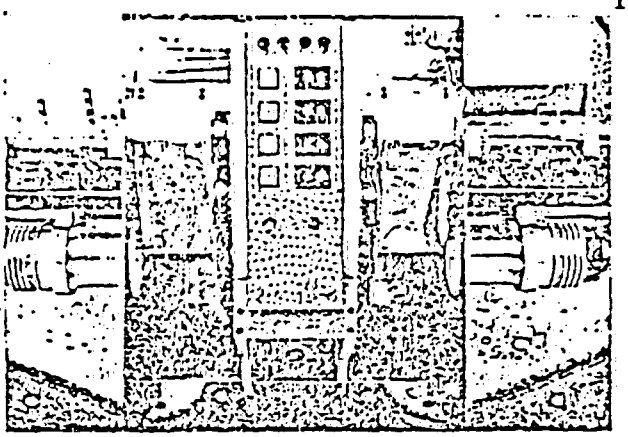


Figure 5. Center panel.



sealed plastic bag contained in a large airtight container. The air displaced from the container may then be measured with a bubble flow meter during each successive puff on the cigarettes. The average of the eight to ten puff volumes may then be calculated. If the puff volume is not 35 cm^3 per two-second puff ± 0.1 (1050 cm^3 per minute ± 3 cm^3), the appropriate adjustment is made to the puff air flow control and the above procedure is repeated.

Since the air flow through the cigarette during a puff is a function of the pressure drop across the cigarette, it is necessary to use cigarettes of a relatively uniform pressure drop in order to maintain the calibrated delivery of smoke. It should be noted that the above calibration gives an average 35 ml per puff delivery over the smoking of the whole cigarette to whatever butt length was used in the initial calibration. Each individual puff may not be 35 ml because the early puffs are taken through a higher pressure drop than the later ones and are therefore somewhat smaller in smoke volume delivered.

It is well known that the pressure drop of a cigarette measured before lighting is somewhat less than after it has been lighted and a coal has been established; however, we have found that a relatively firm relationship between the two values does exist. This makes it possible to estimate the puff air pressure which will be required for proper puff volume by knowing the unlighted cigarette pressure drop. This estimate can be used in initially setting up the machine for a particular cigarette sample prior to the actual puff volume calibration. This calibration then needs to be repeated only when a change is made to cigarettes of significantly different pressure drop.

Figure 1 shows the machine's front panel where the operating controls are located. The air pressure gauges and associated control knobs on the right hand panel (Figure 4) are used to obtain the proper puff volume and air dilution ratio.

The four top toggle switches and the four programmable counters in the center panel (Figure 5) control the function of an automatic switching valve located at the exit port of the shuttle valve. This switching valve routes the smoke from the shuttle valve outlet to any or all of the four animal exposure chambers, in sequence, for the number of seconds indicated on the respective counters. The top toggle switches are used to select which exposure chambers should receive smoke. The white toggle switch below the counters can be set in either the A-mode or B-mode position. When in A-mode position, the sum of the times from the activated counters may not be more than 60 seconds. This insures that smoke from each puff of the cigarette will go to each animal holder. That is, each animal holder will get smoke from the first puff of the cigarettes during its first exposure, from the second puff of the cigarettes during its second exposure, etc. If the sum of the times is less than 60 seconds, the smoke generated during the remaining time of each puff cycle will be vented out through the central column and exhausted by a fan incorporated within it. The black toggle switch at the lower left of the center panel operates this exhaust fan.

When the white toggle switch is in the B position, any combination of exposure times up to 99 seconds each may be set into the counters and the respective exposure chambers will receive smoke for the selected number of seconds in turn. It should be noted, however, that if the total of the times selected exceed 60 seconds, not all chambers will receive smoke from the same puff of the cigarette. This may or may not be important depending upon the design of the animal experiment being carried out.

In addition to directing the flow of smoke among the various exposure chambers according to the selected schedule, the switching valve also directs breathing air to the chambers between smoke exposures. This air supply begins immediately when the smoke to a particular chamber is stopped and is supplied at the same flow rate as the smoke had been previously.

Adjustments within the valve itself allow the researcher to select different degrees of smoke dilution for each chamber if he so desires. The available range of smoke concentrations is from 5% smoke to 20% smoke and is set by means of individual needle valve adjustments.

The left hand panel contains the controls used to

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start and stop the machine, to determine the number of cigarettes to be loaded, and the number of puffs to be smoked on each cigarette. The lighted display at the top of this panel shows the current status of the machine; that is, the number of cigarettes remaining to be puffed in the current cycle and the number of puffs remaining to be taken on each cigarette. This display also tells which functions are currently being performed by the machine such as loading cigarettes, lighting cigarettes, puffing, or ejecting butts. A warning light, also in this display, will appear if there is a malfunction of the machine.

The push-button switches to the left side of the left hand control panel are the start, stop and reset switches. If it is necessary to stop the machine for any reason while it is in operation, this can be done by simply pressing the stop switch. Two options are then available for restarting the machine. Pressing the start switch will restart the operations from where ever in the sequence they were stopped or if one desires to start over from the beginning, this is accomplished by pressing the reset switch followed by the start switch. The machine will then start in the loading and lighting cycle.

The round selector switch in the center of the left hand panel is the main power switch for the machine and is used to select stand-by, single cycle, or multiple cycle modes or to put the machine in test mode. Moving this selector from off to stand-by supplies power to all of the electrical circuits of the machine but does not start any of the operations. The single cycle mode setting will, after pressing the start switch, allow the machine to operate through one complete cycle of loading, lighting, smoking and ejecting. The machine will then automatically stop. If the multiple cycle mode is selected, the machine will automatically start a second, third, etc. cycle as soon as the previous one has been completed. In this mode, new cigarettes are loaded and lighted as old ones are being ejected so that there is no break in the supply of smoke to the switching valve. The cigarettes are supplied from cartridge type magazines which can be filled off the machine and inserted by the operator during each cycle to provide cigarettes for the next loading.

The two programmable counters at the right of the left hand panel are used to select the number of puffs to be taken on each cigarette during each complete machine cycle and to select the number of cigarettes to be loaded during each cycle. The maximum number of cigarettes which can be loaded for each cycle is, of course, 30 and the maximum number of puffs per cigarette is determined by the burning rate of the particular cigarettes being used in the experiment and the butt length desired. A minimum butt length of about 25 mm should be observed to prevent possible damage to the cigarette holders and to assure proper operation of the butt ejecting device.

With the mode selector knob in the test position, a series of test circuits are activated which are controlled by individual function switches located on the back of the smoking machine. They are included as an aid to trouble shooting in case of machine malfunction. As stated earlier, the machine is controlled primarily with digital logic circuits. The electrical components responsible for each function are located on printed circuit boards so that should trouble develop with a certain function, that board can be quickly replaced. Each function such as right puff chamber, left puff chamber, right loader, left loader, right ejector, left ejector, etc. has its own switch on the back of the machine so that each can be operated separately in the test mode, thus making it easy to isolate a source of trouble.

A similar arrangement is provided for all pneumatic functions through appropriate test circuits also located on the back panel. The components which control the various pneumatically activated functions are grouped so that the components responsible for each function are included in a plug-in module, analogous to an electronic circuit board, so that it can be quickly removed and replaced if trouble develops within it. Arrangements have been made with an instrument manufacturer (3) to make the machine described here, and a simpler, less sophisticated model available commercially. Any inquiries regarding availability should be directed to this manufacturer.

RESULTS AND DISCUSSION

In order to establish that the smoke produced by this reverse smoking technique is equivalent to that produced from the same cigarettes by the vacuum puffing method, a number of chemical parameters were measured on the smoke produced by this machine and a standard analytical smoking machine using Kentucky Reference 1R1 cigarettes.

In order to be sure that the calibration of the puff volume to an average value of 35 ml per puff over eight puffs was a valid approximation of the standard analytical smoking procedure, tar and nicotine deter-

Table 1. Tar and nicotine analyses.

Parameter important depending upon the design of the smoker	30-Port smoker		Phipps & Bird smoker	
	Mean	Standard deviation	Mean	Standard deviation
Cigarette weight (g)	1.130	.0057	1.130	.0057
Pressure drop (mm H2O)	68.0	2.15	68.0	2.15
Water (mg/cig.)	2.6	.38	2.6	0.11
Dry particulate material* (mg/cig.)	22.5	3.19	23.4	0.71
Nicotine (mg/cig.)	1.83	0.102	1.71	0.07
Corrected particulate material** (mg/cig.)	21.2	3.83	21.4	1.25
Number of puffs	8		8	

* D.P.M.: The material collected on a Cambridge filter pad less water.

** C.P.M.: The material collected on a Cambridge filter pad less water and nicotine, and often referred to as "tar".

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Table 2.

	4,4-Dichlorobenzophenone (DBP) (µg)
1. Apparatus, undiluted smoke	862
2. Apparatus, diluted smoke	90
3. Total smoke	20 050

Loss of DBP in apparatus : 4.3 % (undiluted)
Loss of DBP in apparatus : .45 % (10 % smoke)
The loss of DBP represents the loss of particulate matter.

minations were performed on a group of carefully selected 1R1 cigarettes. A group of cigarettes was selected by weight (within ± 10 mg of the mean weight) and by pressure drop (within ± 5 mm of the mean pressure drop) after having been conditioned for 24 hours at 75° F and 60% relative humidity. This group was then divided into two groups, one for smoking on the standard Phipps and Bird analytical smoker and one for smoking on the 30-port reverse smoking machine. Ninety cigarettes were smoked on the latter machine and the condensate collected on 20 previously weighed Cambridge filter pads positioned around a 20-port manifold. The other group (100 cigarettes) was smoked according to the standard Federal Trade Commission (FTC) procedure on the Phipps and Bird 20-port machine. The analyses for tar, nicotine, and water were carried out according to the FTC methods (Table 1).

Deposition within the apparatus was assessed by smoking cigarettes containing 3880 ± 466 µg 4,4-dichlorobenzophenone (DBP) and comparing the amount extracted from the apparatus to that retained on the filter pad. The analytical procedures involved have been reported previously (4). The data in Table 2 represents two determinations, one conducted with whole smoke alone and one in which the smoke was immediately diluted to 10% concentration with air. A dramatic decrease in deposition, as measured by this method, takes place when the smoke is diluted.

The determination of several fixed gases was carried out using 1R1 cigarettes in the machine reported here and compared to the results produced by a single port syringe type smoking machine. Thirty 1R1 cigarettes were smoked eight puffs each on the reverse puff machine using a dilution ratio of 9 parts air to one part smoke, giving a total volume of 84 liters. The total gases generated were collected in a Tedlar® (polyvinyl fluoride) bag after passing through a 142 mm diameter Cambridge filter pad to remove the particulate matter. Samples of the contained gas were then introduced into the gas sampling loop of a gas chromatograph and analyzed for carbon monoxide, carbon dioxide, oxygen, nitrogen, and methane (5).

The results are presented in Table 3 along with the results obtained similarly from 1R1 cigarettes smoked 8 puffs on a single port syringe type smoker similar in operation to the multiport Phipps and Bird analytical smoking machine.

In a separate experiment, gas was collected from the exhaust manifold of the Phipps and Bird analytical smoking machine and analyzed for carbon monoxide and carbon dioxide. Since the degree of dilution due to dead volume within the apparatus was unknown, the percentages or absolute yield per cigarette of these gases could not be calculated from the analysis; however, the ratio of CO/CO_2 was determined to be 0.492 ± 0.003. A similar determination made using gas phase generated by the 30-port reverse smoking machine described above gave a CO/CO_2 ratio of 0.475 ± 0.002.

Mikami et al. (6) have reported data indicating that the CO/CO_2 ratio is a rather sensitive indicator of puff volume. They determined this ratio to be 0.50 for the standard 35 cm^3/2-second puff regime.

The values for 4.1 % by volume CO and 8.6 % CO_2 determined from the gas sample from the reverse smoker agree well with those for 1R1 cigarettes reported by *Guerin* (7). His analysis gave 4.5 % CO and 8.4 % CO_2.

A number of polycyclic hydrocarbons were analyzed in smoke condensate generated by the 30-port reverse smoker for comparison with similar data obtained on tar from a vacuum type machine (Borgwaldt Model M 9). The condensates collected for these analyses were collected in cold traps at dry ice temperature and were subsequently dried by codistillation of the water with acetone at 40° C under vacuum. The data in Table 4 is expressed in terms of gas chromatographic peak area units. These units can be converted to weight units by application of the appropriate response factors, but this was not done since the purpose of the analysis was

Table 3. Fixed gases from 1R1 cigarettes.

Machine type	No. of puffs	Milligrams per cigarette*				
		CO	CO_2	O_2	N_2	CH_4
30-Port reverse smoker	8.0	13.91 ± .34	45.24 ± 0.78	44.19 ± 0.8	214.31 ± 0.82	1.08 ± 0.03
Syringe type smoker	8.0	16.50 ± .40	46.19 ± 4.04	44.93 ± 1.17	221.25 ± 3.27	1.03 ± 0.10

* Replicate determination, ± one standard deviation. Data not corrected for thermal conductivity response factors.

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Compound	Units per gram condensate corrected to 100 % recovery	
	30-Port reverse smoker	Borgwaldt smoker
Benzanthracene	198	186
Chrysene	297	307
Benzofluoranthrenes	81.6	82.0
Benzo(e)pyrene	39.6	38.3
Benzo(a)pyrene	59.4	54.8
Indole	$466 \cdot 10^3$	$492 \cdot 10^3$
3-Methylindole	$352 \cdot 10^3$	$338 \cdot 10^3$
3-Ethylindole	$95 \cdot 10^3$	$93 \cdot 10^3$
Carbazole	$35 \cdot 10^3$	$25 \cdot 10^3$

only to compare the composition of the condensates from the two types of smoking machines. In each case, radiocarbon labeled benzo(a)pyrene was added to allow the calculation of the percent recovery of benzo(a)-pyrene in the analysis. All of the polycyclic aromatic compounds reported have been corrected by the factor determined for benzo(a)pyrene recovery. The indole type compounds have not been corrected for recovery and are reported directly as measured.

Gas chromatographic analysis of some of the condensable gas phase components of smoke from 1R1 cigarettes smoked on the 30-port reverse smoker and on a single port syringe type smoker was carried out by the method reported by *Spears* et al. (8). The results in Table 5 indicate that the gas phase compositions with respect to those materials analyzed was not significantly different between the two types of smoking machines.

CONCLUSIONS

The above data show that, within the expected analytical error of the methods involved in the various measurements, the smoke produced by the two different types of smoking is not chemically different. Because of the ability of the smoking machine described here to generate a continuous stream of smoke at one or several preset dilution ratios and because of the various automatic functions incorporated, one machine of this type could be used to support an animal inhalation experiment using as many as 2000—5000 mice, depending upon the exposure regime chosen.

SUMMARY

Experience gained from a recent evaluation of smoking machines has been applied in the design of a sophisticated automatic smoking machine. Utilizing a reverse puff mechanism, a continuous or intermittent smoke stream is generated, diluted to selected concentration levels and channelled to multiple exposure apparatus. All functions are completely controlled by digital electronics as is the detection of faults in the system. Analysis of the smoke produced indicates that it is not chemically different from the smoke delivered by other types of apparatus.

Table 5. Comparison of gas phase from two types of smoking machines.

Compound	30-Port reverse smoker	Single port syringe smoker
Isoprene	3533*	3328*
Acetaldehyde	1814	1937
Acetone	2487	2258
Acrolein	443	567
2-Methylfuran	381	402
Benzene	710	740
Ethanol	504	561
Toluene	1124	1210

* All data are given in arbitrary units representing areas under chromatographic peaks.

ZUSAMMENFASSUNG

Die Erfahrungen aus einer kürzlich durchgeführten Bewertung von Rauchmaschinen wurden beim Entwurf einer hochentwickelten automatischen Rauchmaschine angewandt. Unter Benutzung des Druckverrauchens wird ein kontinuierlicher oder intermittierender Rauchstrom erzeugt, auf gewählte Konzentrationen verdünnt und verschiedenen Apparaturen zugeleitet. Alle Funktionen einschließlich der Aufdeckung von Störungen werden vollständig durch Digitalelektronik kontrolliert. Die Untersuchung des erzeugten Rauches zeigte, daß dieser sich chemisch von dem Rauch anderer Maschinentypen nicht unterscheidet.

RESUME

Les données d'une étude récente de différentes machines à fumer ont été appliquées dans la conception d'une nouvelle machine à fumer automatique très perfectionnée. En utilisant un mécanisme de bouffée inversée, un flux de fumée continu ou intermittent est généré, dilué à des concentrations préalablement établies, et dirigé vers un appareil à expositions multiples. Toutes les fonctions sont complètement contrôlées par touches électroniques, ainsi que la détection des erreurs dans le système. L'analyse de la fumée produite montre qu'elle n'est chimiquement pas différente de la fumée produite par d'autres machines.

REFERENCES

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2. Morrissey, C. A.: Cigarette smoking machine; U.S. Patent Specification No. 3, 528, 439.

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CIGARETTE SMOKE TRACERS: GAS CHROMATOGRAPHIC ANALYSIS OF DECACHLOROBIPHENYL

Summary

Decachlorobiphenyl in microgram quantities was used as a tracer for estimating the deposition of total particulate matter of cigarette smoke in the airways of laboratory animals. This compound, because of its lack of transfer to the pulmonary circulation, is useful as a tracer of total smoke exposure. On the contrary, because of its rapid transfer to the blood, dichlorobenzophenone is best used as a tracer for estimating deposition of smoke in non respiring airways and the study of clearance by mucociliary transport.

Previously, the use of 4,4'-dichlorobenzophenone (DBP) as a tracer for water-insoluble particulate components of tobacco smoke was described.[1] Further studies indicated that the quantity of halogenated tracer found in the respiratory tract of laboratory animals is not only a function of well known clearance mechanisms but also a function of transfer into the blood. It is probable that transfer into the blood can occur at a very rapid rate for many water-insoluble chemical compounds administered by inhalation.

This report presents a sensitive analytic method for decachlorobiphenyl (DCBP) in the animal lung and in the particulate matter of smoke derived from labeled cigarettes. Data are presented for several experiments demonstrating the utility of this tracer. Also, data are presented which indicate that a fraction of the DBP tracer transfers quickly to the blood, whereas DCBP tracer is not transferred in the same time interval.

Data relating to rapid transfer from the lung to the pulmonary circulation of a number of other halogenated compounds are also presented.

Basically, the same methods previously reported[1] for preparing cigarettes, smoking sample cigarettes, exposing animals, and of analysis of tissue, were used in these experiments, except for the conditions of gas chromatography.

For the analysis of DCBP, each tissue sample was homogenized in a semimicro Waring blender jar with 1 ml of a hexane solution containing 1 μg of the internal standard 1,1'-dichlorodiphenyldichloroethane (DDD) per ml. 15 ml of hexane, and 12 g of anhydrous sodium sulfate. The resulting mixture was treated as described previously for tissues containing DBP.

The gas chromatographic conditions for analysis of DCBP were similar to those for analysis of DBP except for the following changes: (*1*) injection port temperature, 285° C; (*2*) column temperature, 260° C; (*3*) electron capture detector temperature, 300° C; (*4*) glass tubing column 1.2 m long by 6 mm in diameter, packed with 3.9 per cent UCW-98 silicone rubber on 80-100 mesh Supelcoport.[2]

The calibration curve for DCBP is shown in figure 1. Recovery of DCBP was 100 per cent when 0.2 to 3.0 μg of DCBP was added to the samples.

Tissue samples containing DDD and 4,4'-dibromodiphenylmethane (DBDM) were analyzed by the previously reported method for DBP[1] using DBP as the internal standard. Calibration curves for each analysis resembled those for DBP.

The data from an experiment with Long-Evans strain rats exposed to eight 40-second puffs of smoke at a rate of one puff per min from DCBP-labeled cigarettes (0.217 per cent DCBP by weight of tobacco, yielding 250 μg of DCBP in the mainstream smoke per cigarette), diluted 6 to 1 with air are shown in table 1 with data from an identical experiment in which DBP cigarettes were used (0.360 per cent DBP by weight of tobacco, yielding 500 μg of DBP in the mainstream smoke per cigarette). In both cases, the lung and trachea of the animals were excised within approximately 2 minutes after exposure. It was found that the lung deposition of DCBP in per cent (13.4 per cent of theoretic) was greater than that for DBP (0.18 per cent of theoretic). Similar results were obtained with hamsters and

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[1] Lewis, C. I., McGeady, J. C., Wagner, J. R., Schultz, F. J., and Spears, A. W.: Amer. Rev. Resp. Dis., 1972, *106*, 480.

[2] Supelco Products, Inc., Bellefonte, Pennsylvania 16823

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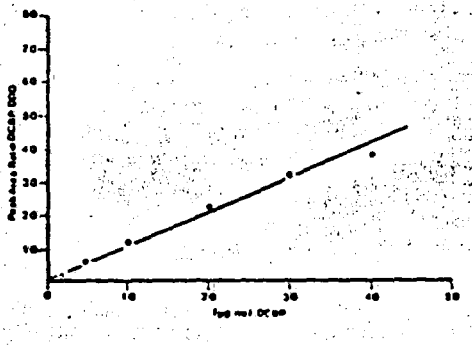

Fig. 1. Calibration curve for analysis of decachlorobiphenyl.

mice. This difference in the fraction of the 2 tracers found in the lung could not be explained by extrapolation of the DCBP tracer clearance curve to zero time as depicted for DBP in the previous study[1]; therefore, it was the result of unusually high disappearance of DBP within 2 minutes after exposure.

To elucidate this rapid clearance, anesthetized, tracheotomized rats were administered labeled smoke generated by a 35-ml puff taken with a syringe in approximately two seconds from the cigarette. By use of a 3-way valve, a 4-ml aliquot of the fifth puff was administered to the animal and a 16-ml aliquot of the sample puff was collected on a Cambridge filter for analysis of the tracer delivered to the animal. After administration of smoke, the trachea was clamped and the lung was excised within 2 minutes. In one type of experiment, laparotomized rats were used in which pneumothorax was produced by a diaphragmatic hernia immediately before administration of smoke. Strong heart beats were maintained during administration of smoke. In another type of experiment, freshly isolated, cannulated, rat lungs were exposed to smoke in a similar manner. The results indicated that the fraction of tracer recovered in a given animal species was a function of molecular weight, and probably molecular size and solubility (table 2). The heaviest (DCBP) and lightest (DBP) mole-

TABLE 2

MEAN RECOVERY OF CIGARETTE SMOKE TRACERS FROM ANESTHETIZED, CANNULATED INTACT RATS WITH PNEUMOTHORAX AND ISOLATED, CANNULATED RAT LUNG-TRACHEA PREPARATION*

Tracer†	Molecular Weight	Lung-Trachea	Recovery
DBP	251	Isolated	83
DBP	251	Intact	11
DDD	320	Intact	40
DBO	326	Intact	64
DCBP	499	Intact	104

*Adult, Long-Evans strain rats. Undiluted smoke (35 ml per 2-second puff) was generated and delivered with a syringe, and the fifth puff was used.

†DBP = 4,4'-dichlorobenzophenone; DDD = 4,4'-dibromodiphenylmethane; DCBP = decachlorobiphenyl; DBO = 4,4'-dibromodiphenylmuthane.

TABLE 1

MEAN VALUES OF DEPOSITION OF CIGARETTE SMOKE TRACERS, 4,4'-DICHLOROBENZOPHENONE (DBP) AND DECACHLOROBIPHENYL (DCBP) IN LUNGS OF MALE ANIMALS

Animals*	Tracer	Concentration In Diluted Smoke (μg/ml)	Total Exposure Time (min)	Estimated Ventilation† (ml/min)	Lung Deposition (μg)	Lung Deposition (%)**	DCBP/DBP (%)
Rat (a)	DBP	0.301	5.33	174	1.3	0.48	
Rat (b)	DCBP	0.127	5.33	160	14.5	13.4	28
Hamster (c)	DBP	0.301	5.33	44	0.32	0.46	
Hamster (d)	DCBP	0.127	5.33	70	4.4	9.4	20
Mouse (e)	DBP	0.180	2.40	25	0.05	0.46	
Mouse (f)	DCBP	0.009	2.40	29	0.69	11.1	24

*(a)(b): Ten of 360 g and 4 of 320 g Long-Evans rats per group, respectively.
(c)(d): Twenty of 60 g and 4 of 110 g Golden Syrian per group, respectively.
(e)(f): Twenty of 28 g and 10 of 38 g ICR per group, respectively.

†Calculated according to Guyton.[8]

**Amount of tracer remaining in lung times 100 divided by the amount in inspired air.

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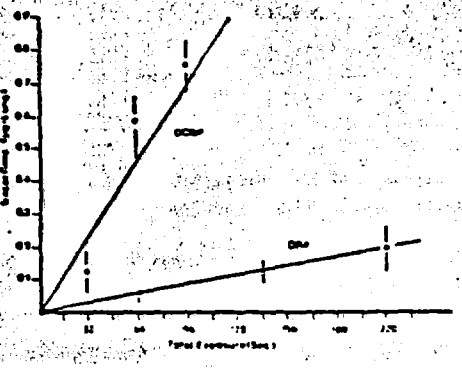

Fig. 2. Concentration of decachlorobiphenyl and 4,4'-dichlorobenzophenone in the lung-tracheal system with increasing smoke exposure time.

cules showed the highest (104 per cent) and lowest (11 per cent) recoveries, respectively. There was a great difference in the per cent recovery of the tracer DBP in the isolated (83 per cent) and intact (11 per cent) lungs (table 2). Because the pulmonary circulation was intact during delivery of noke in the intact preparation, it appeared that the rapid loss of the tracer from the respiratory tract was to the bloodstream. The ratios of deposition of DCBP to deposition of DBP in per cent in lung for the rat, the hamster, and the mouse were 28, 20, and 21 per cent respectively (table 1).

The tissue concentrations of both tracers increased linearly as a function of exposure time (figure 2). Data on pulmonary clearance of both tracers 2 minutes after exposure in a double-labeling experiment in the rat are shown in figure 3 together with clearance data for *E. coli* from the literature.[3]

The fractions of the DBP and DCBP found in the head and stomach-esophagus were of approximately the same order of magnitude, whereas the fractions of DBP and DCBP found in the lung trachea differed more than one order of magnitude (table 3). From these data, and from those presented in figure 2, it was concluded that the DBP that was deposited on inhalation in the respiring area of the lung was transfered to the blood very quickly.

The DCBP found 2 minutes after exposure

[3] Rylander, R.: Acta Physiol. Scand., 1968 (Supplement *306*, p. 77).

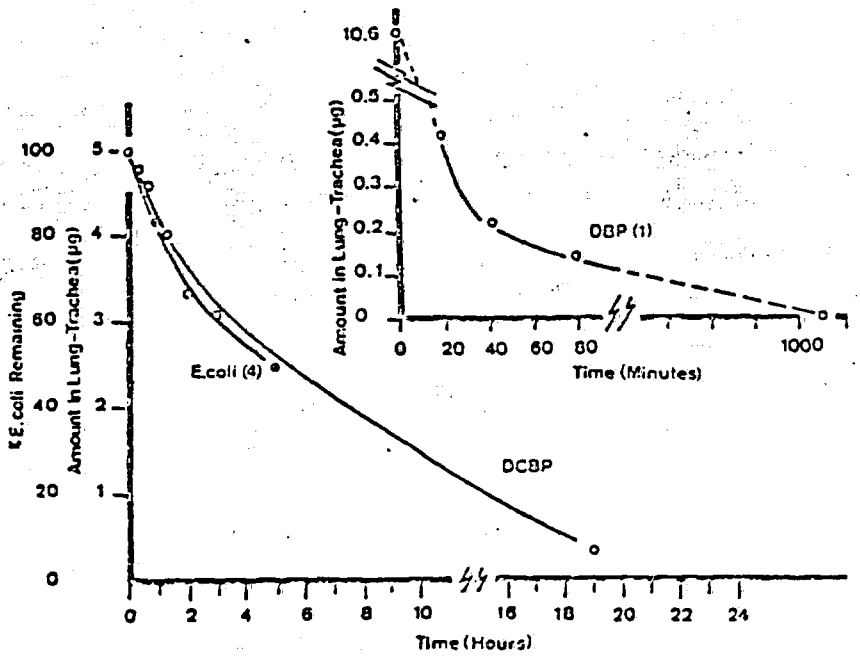

Fig. 3. Rate of clearance of decachlorobiphenyl from the lung tracheal system compared with clearance of *Escherichia coli*[3] and 4,4'-dichlorobenzophenone (DBP).[1]

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TABLE 3

DEPOSITION OF CIGARETTE SMOKE TRACERS 4,4'-DICHLOROBENZOPHENONE (DBP) AND DECACHLOROBIPHENYL (DCBP) IN MOUSE ORGANS AFTER EXPOSURE TO DOUBLY LABELED SMOKE*

Organ	Tracer†	Conc. in Diluted Smoke (μg/ml)	Total Exposure Time (sec)	Deposition (μg)	Deposition (%)**
Stomach-esophagus	DBP	0.30	144	0.45	2.2
Lung-Trachea	DBP	0.30	144	0.10	0.48
Head††	DBP	0.211	96	0.41	4.2
Stomach-esophagus	DCBP	0.089	144	0.18	2.9
Lung-Trachea	DCBP	0.089	96	0.76	18.4
Head††	DCBP	0.089	96	0.38	9.2

*Mean values of 20 ICR strain male mice (26 g). Ventilation equals 29 ml.[7]

†See table 2 for definitions of abbreviations of compounds.

**Amount of tracer remaining in organ times 100 divided by the amount in inspired air.

††All skin removed.

represents the total quantity deposited in the respiratory tract; the clearance rate was similar to that previously attributed to a combination of mucociliary transport and macrophage activity.[4,5] It is noteworthy that the fraction of *E. coli* (approximately 10 per cent) cleared by mechanical transport was of the same order of magnitude as the fractional ratio of DBP to DCBP found in the respiratory tract 2 minutes after exposure. This is consistent with the suggestion that DBP is recovered only from the nonrespiring portions of the lower respiratory tract.

• • •

Vaughan[6] reported the total retention of radioactive sodium chloride-glycerine aerosols of varying sizes in the lungs of anesthetized rats. For a 0.6-μm aerosol, which is an approximation of the mean particle size for cigarette smoke,[7] the retention was 14 per cent. Using an estimated ventilation of 160 ml per min for the rats (table 1) and the data for the DCBP tracer,[8] the retention of 6:1 diluted smoke was estimated to be 13.4 per cent.

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INHALATION TOXICITY STUDIES ON CIGARETTE SMOKE
II. TOBACCO SMOKE INHALATION DOSIMETRY STUDIES ON SMALL LABORATORY ANIMALS

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SUMMARY

A newly developed exposure system has been used to carry out smoke dosimetry studies on rats, mice, hamsters and guinea pigs. In all species, smoke total particulate matter (TPM) deposited in significant amounts in the lower respiratory system (LRS) at dose levels ranging from 0.515 to 1.710 mg TPM/g respiratory tissue.

Nasal deposition of smoke particulates did occur in all of the species examined.

The significance of these dosimetry data in relation to the conduct of long-term comparative inhalation toxicity studies with tobacco smoke is discussed.

INTRODUCTION

Experimental techniques for smoke inhalation studies are still being developed and several problems in this field remain to be investigated more fully. These include, for example, the choice of species for inhalation work, characterisation of smoke particulate deposition in various regions of the respiratory system of animals and smoke dosimetry studies on small species under standard conditions.

A programme was designed to investigate some dosimetry problems and to evaluate a new exposure system [1]. A large proportion of the work in-

* Requests for reprints to Dr. Binns.

Abbreviations: COHb, carboxyhaemoglobin; DCBP, decachlorobiphenyl; LRS, lower respiratory system; TPM, total particulate matter.

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volved exposure of rats to smoke from different cigarettes under varying conditions [2]. As part of the evaluation, it was considered worthwhile to carry out a number of experiments on rats, golden hamsters, mice and guinea pigs exposed to smoke from the same cigarette type, using the same exposure system, smoke concentration and duration of exposure throughout. It was hoped that such a comparison of species would throw some light on aspects of the more basic problems of smoke toxicity work referred to above.

MATERIALS AND METHODS

A new exposure system [1] was used for this work. During exposure animals were fitted in pairs on to the central exposure chamber in plethysmograph-type restraining tubes, the sizes of which were appropriate to the species being used. A 70 mm plain cigarette containing flue-cured tobaccos was used. Delivery of TPM from the cigarette was 41.9 mg/cigarette. During exposures smoke was generated under standard conditions (35-ml puff, 1 puff/min, to a standard butt length of 23 mm) and diluted 1 in 14 (smoke : air, v/v) before passing to the exposure chamber of the inhalation machine. Diluted smoke filled the chamber throughout the whole of the exposure period.

The technique for assessing deposition of TPM in the respiratory system of animals was based on the use of DCBP as a particulate phase marker [3]. Cigarettes were spiked with DCBP and suitably conditioned before being used. Animals, which were not preacclimatized to smoke, received a single 10-m exposure to smoke from cigarettes containing DCBP.

Following exposure, animals were rapidly killed and tissues removed for analysis of DCBP, hence TPM, retained in the various regions of the respiratory system. The respiratory system was divided into 5 regions: (*i*) skinned head (less brain), (*ii*) skinned lower jaw and tongue, (*iii*) larynx, (*iv*) trachea, and (*v*) main bronchi and lungs. Details of the analytical techniques for detection of DCBP in tissue samples have been given elsewhere [2]. COHb levels in blood samples taken immediately following exposure were determined using an IL CO-Oximeter (Instrumentation Laboratories Ltd.).

RESULTS

Monitoring of the exposure system showed that between the butt end of the cigarette and the entrance to the exposure chamber there was loss of 10.3% of TPM leaving the cigarette in mainstream smoke. During exposures the average chamber smoke concentration was 7.67 mg/l.

Amounts of TPM deposited in various regions of the respiratory system of the animals exposed under similar conditions and mean COHb levels are shown in Table I. The values for stomach samples are shown for 3 of the 4 species.

The particulate phase marker was detected in all respiratory system samples taken from all species exposed to smoke containing DCBP. For any species mean TPM deposition was always heaviest in the lungs of the ani-

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TABLE I

MASS DISTRIBUTION OF TPM IN DIFFERENT SPECIES FOLLOWING 10-min EXPOSURE TO DILUTED CIGARETTE SMOKE

Figures shown for each species are mass mean deposition (S.D.), and % of total respiratory system deposition.

Species	Number of aminals	Mean body weight (g)	Head (μg) (%)	Lower jaw (μg) (%)	Larynx (μg) (%)	Trachea (μg) (%)	Lungs (μg) (%)	Total [a] respiratory system (μg)	Stomach (μg)	Blood [b] COHb (%)
Rat	6	214	83.06	64.5	47.9	34.8	596.1	826.4	—	26.5
		(49)	(42.6)	(21.0)	(48.8)	(19.5)	(254.2)	(254.3)	—	(8.1)
			10.0	7.8	5.8	4.2	72.1			n = 10
Mouse [c]	5	17	106.9	37.7	14.8	5.3	228.4	393.2	40.0	61.3
		(1)	(27.7)	(20.7)	(10.6)	(2.5)	(87.2)	(69.6)	(14.3)	(4.6)
			27.2	9.6	3.8	1.4	58.1			n = 5
Golden hamster	6	101	106.9	35.6	44.8	27.9	526.0	740.9	302.0	44.1
		(2)	(62.0)	(41.5)	(41.7)	(30.1)	(198.7)	(278.5)	(139.3)	(10.2)
			14.4	4.8	6.1	3.8	71.0			n = 8
Guinea pig	5	321	245.5	29.3	25.1	32.0	1836.5	2168.5	57.3	34.4
		(22)	(56.7)	(20.1)	(9.3)	(7.4)	(328.4)	(328.4)	(58.7)	(3.9)
			11.3	1.4	1.2	1.5	84.7			n = 7

[a] Head, lower jaw, larynx, trachea, lungs.

[b] Mean includes values for extra animals exposed to 'blank' cigarettes.

[c] 3 animals died during the exposure.

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mals, showing effective penetration of smoke particulate phase into the distal parts of the respiratory system.

Calculation of a simple distribution pattern shows that TPM deposition in the upper respiratory system was to be most marked in the mouse (36.8%), least marked in the guinea pig (12.7%) and intermediate between these extremes in rats (17.8%) and hamsters (19.2%). It is interesting to note that in all species except the rat, TPM deposition was more marked in the head (predominantly nasal) than the lower jaw (predominantly oral) region. In the rat, this difference of TPM deposition in the two regions of the head was less pronounced.

It is not particularly useful to compare directly absolute TPM loads in the various tissues from the four species as shown in Table I, because of differences in bodyweight and hence distinct differences in tissue weights in various animals. It is probably more appropriate to express TPM dose in terms of a unit weight for each of the various lower respiratory tissues. This makes comparison of the dose level achieved in the different species more meaningful. Obviously, TPM dose to head regions expressed as particulate weight per unit weight of tissue would not be at all useful. Table II shows summary TPM dosimetry information for the LRS only, for the 4 species.

If the LRS is considered as a whole, TPM loading per unit weight of tissue was highest in the mouse and lowest in the rat, with the hamster and guinea pig showing a very similar intermediate dose level. Because most particulate marker was always detected in the lungs of all animals, this species ranking applies also to lung-only deposition. The calculated TPM dose to the larynx and trachea was apparently much more variable, due at least in part to the lower absolute amount of TPM marker present in these regions and the larger

TABLE II

MEAN TPM DOSE (AS μg/g TISSUE) FOR VARIOUS REGIONS OF THE LOWER RESPIRATORY SYSTEM (LRS [a]) IN RATS, MICE, GOLDEN HAMSTERS AND GUINEA PIGS

Figures shown for each species are mean and (S.D.)

Species	Larynx (μg/g)	Trachea (μg/g)	Lungs (μg/g)	LRS (μg/g)
Rat	442.9 (360.0)	310.6 (119.0)	549.4 (290.7)	515.2 (250.5)
Mouse	1873.6 (1180.5)	437.4 (269.6)	1798.9 (535.8)	1710.3 (465.4)
Golden hamster	754.8 (677.6)	859.0 (900.3)	986.1 (363.7)	970.8 (388.3)
Guinea pig	213.2 (144.5)	275.7 (99.5)	1061.4 (207.3)	946.7 (211.0)

[a] larynx + trachea + lungs.

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TABLE III

FOR 4 SPECIES, THE RATIO OF HIGHEST TO LOWEST TPM DOSE (AS μg/g OF TISSUE) DETECTED IN VARIOUS REGIONS OF THE LOWER RESPIRATORY SYSTEM

Species	Larynx	Trachea	Lungs	Total LRS
Rat	12.2	5.3	6.0	3.9
Mouse	6.5	13.6	2.2	2.0
Guinea pig	10.7	3.0	1.7	1.7
Golden hamster	28.8	37.0	3.3	3.8

error inevitable in removing, cleaning and weighing these relatively small tissue samples. Generally, there was no marked indication of heavier dosing of the larynx of animals compared with other respiratory regions. Only in the mouse was the mean TPM dose/g of laryngeal tissue marginally higher than for the lung region.

A simple index of variability of dosing to the various regions is given in Table III. This index confirms that TPM dose to the larynx and trachea was very variable for all species. Variability of dose retained by the lungs was less than for larynx and trachea. If the lower respiratory system is considered as a whole, animals showed a 2- to 4-fold range between highest and lowest TPM dose detected in the complete system. The guinea pig particularly and the mouse showed least variability. In this series at least, the rat and also the hamster showed a similar approximately 4-fold variability in dose level.

Exposure of a range of species under similar conditions produced a range in blood COHb levels. Not surprisingly, direct comparison of blood COHb levels against total respiratory system TPM deposited in animals shows no clear relation between the two factors in the different species. However, it is interesting to compare blood COHb level against TPM dose in the lower respiratory system, expressed as a weight of particulate matter per unit weight of tissue, for those animals for which both values are available. Fig. 1 shows this relationship for *all* species after exposure to smoke.

For any one species the range of COHb levels and TPM dose tended to be limited. If all data are considered together, over the complete range of values the correlation between TPM dose to the LRS and blood COHb level is quite striking and is highly significant ($r = 0.795$, significant at 99.95% level). Fig. 1 is particularly interesting since it is a composite picture for different species with a range of mean bodyweights from 17 to 231 g and absolute TPM deposition levels ranging from roughly 150 μg to 2500 μg in the lower respiratory system.

Three mice died during exposure. Two of these showed the highest COHb

LRS = larynx + trachea + lungs

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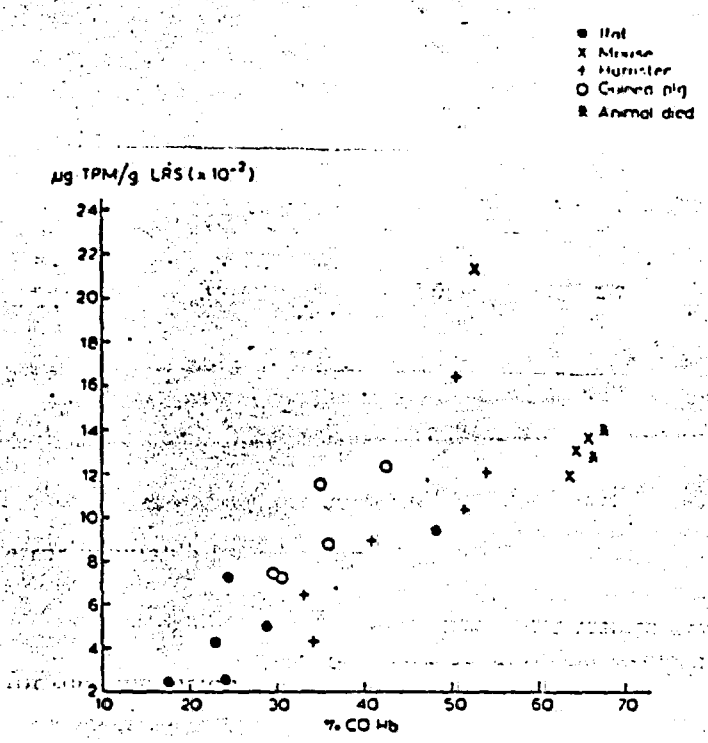

Fig. 1. The relation between TPM dose to lower respiratory system and COHb level in 4 small animal species.

levels recorded in animals, and a high TPM dose to the respiratory system. Whether one of these factors was more important than the other in limiting tolerance to exposure is not clear at present.

DISCUSSION

Information is presented in this paper on dosimetry studies carried out on the more commonly used small laboratory species. In the attempt to deal with several species, information on any particular one is necessarily limited. Yet the results lead to a number of interesting observations.

Effective penetration of smoke beyond the upper respiratory system was achieved in all species tested, with the highest mass deposition of TPM and TPM dose/g of tissue being recorded for lung samples. Deposition of TPM in the head of animals ranged from 12.7% to 36.8% of recorded TPM load in the complete respiratory system of guinea pigs and mice respectively.

The weight of evidence in this paper and in the majority of other studies on smoke particulate distribution in animals (Table IV), suggests that deposition in the head of small species does not seriously impair effective TPM dosing of the lower respiratory system of animals during smoke exposure. Lower respiratory system TPM dose levels recorded in this report were

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TABLE IV

TPM DISTRIBUTION PATTERNS RECORDED FOR THE RESPIRATORY SYSTEMS OF SMALL LABORATORY ANIMALS

Species	Particulate phase marker	Number of animals	% Distribution of marker		Reference
			Head	Lower respiratory system	
Mouse	[^{14}C]hexadecane	8	70.8	29.2	[4]
	DCBP	20	33.3	66.6	[3]
	DCBP	5	36.8	63.2	This paper
Rabbit	^{74}As	6	25.7	74.2 [b]	[5]
Guinea pig	DCBP	5	12.7	87.4	This paper
European hamster	[^{14}C]dotriacontane	2	24.5	75.5	[6]
		29	23.3	77.9	[7]
Syrian golden hamster	[^{14}C]hexadecane	10	48.3	51.7	[8]
	[^{14}C]dotriacontane	2	60.4 [a]	39.6	[6]
	[^{14}C]dotriacontane	29	26.3	73.7	[7]
	DCBP	6	19.2	80.9	This paper
Rat	[^{14}C]dotriacontane	20	23.3	76.7	[9]
	DCBP	6	17.8	82.2	This paper
	DCBP	33	7.3	92.7	[2]

[a] This observation was not confirmed by a more extensive study conducted subsequently [7].
[b] Results probably suspect due to formation of arsine.

highest in the mouse, which also showed the highest percentage TPM deposition in the head.

Significant amounts of TPM were recorded in the lower jaw samples of all species. Rats, which were observed breathing through the mouth during exposure, showed heavy TPM deposition in lower jaw samples. Deposition on the jaw samples compared with the upper part of the head, which contained the nasal region, was less marked though still clear in the mouse and hamster. In the guinea pig, deposition in the head was more predominant in the upper nasal region than in the mouth. There does seem to be both physiological and anatomical evidence that the guinea pig breathes through the mouth only when very severely stressed [10]. Other species may not be obligate nose breathers during smoke exposure, as is often suggested.

Expression of TPM dose per unit weight of respiratory tissue and measurement of blood COHb levels in animals give the opportunity of assessing acute toxicity of smoke in these terms, rather than the more vague but commonly used indices based on percentage dilution of smoke and duration of exposure of animals. More precise methods of doing comparative toxicity

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studies on smoke from different cigarettes, based on exact measurement of dose of smoke to animals, are also a clear possibility.

Data from dosimetry studies on rats and hamsters carried out by another laboratory show TPM dose levels to the respiratory system which compare with those found in our work. Other workers have found TPM doses to rats and hamsters of 0.27 and 0.25 mg/lung respectively, for animals exposed under similar conditions [11]. Guerin and Nettesheim showed clearly that for animals with similar bodyweights there were no major differences in mass TPM deposition in rats and hamsters, if deposition is expressed purely on the basis of TPM/lung.

It is possible to use the above figures to make some estimate if TPM dose/g of lung tissue, using relative lung weights of 0.79% and 0.496% bodyweight [12] for the rat and hamster respectively. The corresponding dose level figures for the two species from the different studies are shown in Table V.

Differences in absolute dose level are no doubt due to differences in exposure system, cigarette type, smoke dilution, exposure regime etc., in the two studies. Values calculated from ORNL data do seem to agree with our finding that for animals exposed under similar conditions, the TPM dose/g lung is greater for the hamster than for the rat. Our work indicated a dose ratio for hamsters : rats exposed under the same conditions of 1.88 : 1, compared with the estimated ratio of 2.06 : 1 from the ORNL figures. If the augmented ORNL figures are accepted as being reasonable estimates of TPM dose level, the two sets of values are remarkably close for relative dose levels obtained in different laboratories using significantly different exposure procedures.

For the combined data from all species, we showed a significant correlation between TPM dose/g of LRS and COHb level. The correlation between TPM dose and COHb level is clear for a range of small animals. Our figures indicate a linear relationship which suggests that no preferential absorption of COHb or deposition of TPM in the lung of animals occurred during exposure. For rats a similar correlation has been shown, with the same level of

TABLE V

TPM MASS DEPOSITION IN LUNGS AND TPM DEPOSITED PER GRAM OF TISSUE IN RAT AND HAMSTER: COMPARISON OF DATA FROM STUDIES CARRIED OUT IN TWO LABORATORIES

Species	Total TPM deposited/lung or (LRS) (mg)		TPM dose/unit weight lung or (LRS) tissue (mg/g tissue)	
	ORNL [a]	This report	ORNL [a]	This report
Rat	0.27	0.68	0.207	0.515
Hamster	0.25	0.60	0.427	0.971

[a] Oak Ridge National Laboratory.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

significance, for lung TPM dose and total respiratory volume during exposure to smoke [11].

Because of the limited number of observations which we have in total, and for the individual species in particular, our results show that TPM dose could be predicted from blood COHb levels only within fairly wide limits. Nevertheless, the relationship between COHb and TPM shown in Fig. 1 is interesting because it covers a number of species. Further work on larger scale would be worthwhile to define clearly for one or for all species the reliability of an estimate of COHb level as an index of TPM dose to the lungs of animals. It is worth pointing out that the precise TPM/COHb relationship is likely to differ according to cigarette type or the system used for exposure of animals.

Under similar conditions of exposure, at least on the particular machine used for our work, TPM dose as μg/g LRS was least in the rat compared with hamsters, guinea pigs and mice. The rat also showed considerable variability in TPM levels recorded in the respiratory system. More extensive observations on rats [2] indicate that a 4-fold range in TPM dose achieved by animals exposed under similar conditions is common for this species.

A limited number of observations on guinea pigs indicate that relatively high TPM dose levels can be achieved in this species. The animal tolerates exposure to smoke extremely well and does not appear to be particularly irritated by smoke, as do all other species. The consistency of dose levels achieved in the guinea pig reflect the behaviour and steady breathing pattern observed for this species during exposure.

Of course, the choice of species for inhalation toxicity studies will not be determined entirely on the basis of dosimetry data. The availability of such information should, however, allow a more rational choice of animal for such experiments.

ACKNOWLEDGEMENTS

We are pleased to acknowledge the excellent technical assistance given by Mr. B.J. Dyas.

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

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INHALATION TOXICITY STUDIES ON CIGARETTE SMOKE
III. TOBACCO SMOKE INHALATION DOSIMETRY STUDY ON RATS

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SUMMARY

Smoke inhalation dosimetry studies have been carried out on rats, using a new exposure system. A range of cigarettes, tobacco types and smoke concentrations was used.

Penetration of smoke into the lungs was clearly demonstrated, and loads of total particulate matter (TPM) of up 1 mg were detected in the lower respiratory system of rats. The mass of TPM deposited was affected by the smoke concentration during exposure.

Deposition of TPM in the head of the rat was low in relation to total respiratory system deposition. A pattern of predominantly lung deposition was achieved under the conditions used for this series of experiments. This pattern was not affected by changes in smoke dilution level, cigarette or tobacco type.

INTRODUCTION

The rat is currently being used extensively in a number of laboratories carrying out inhalation toxicity studies with tobacco smoke. The work reported in this paper is concerned with particulate deposition in rats subjected to smoke in a new inhalation machine.

The aim of the work was to determine particulate deposition levels in rats subjected to diluted smoke under varying conditions. Some of the variables which were examined in this series of experiments included the effect of

* Request for reprints to Dr. Binns.

Abbreviations: COHb, carboxyhaemoglobin; DCBP, decachlorobiphenyl; DDD, p,p'-dichlorodiphenyldichloroethane; TPM, total particulate matter.

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cigarette and tobacco type, smoke dilution level and the sex of the animal on the deposition of smoke particulates in the respiratory system.

Although a limited amount of information on dosimetry is beginning to emerge, more basic work needs to be done on what is now considered to be an increasingly important aspect of inhalation toxicity studies with tobacco smoke. At this stage, the fairly extensive data presented below added to our present knowledge on smoke particulate deposition in the rat, provide a background for further studies and for comparison of data from other laboratories.

MATERIALS AND METHODS

The exposure system used has been described in detail elsewhere [1]. During exposure of animals smoke was generated under standard conditions and diluted to the desired level before passing to the exposure chamber of the inhalation machine. Diluted smoke filled the chamber throughout the whole of the exposure period.

Rats were obtained from Anglia Laboratory Animals (Wistar derived, strain CFHB) and maintained using conventional procedures. During exposure animals were fitted in restraining tubes, usually in groups of three, around the central exposure chamber.

The cigarette types used, their general characteristics and the exposure conditions selected are shown in Table I. Smoke dilutions were selected at particular levels based on a simple proportion of whole fresh smoke to air. The levels shown in the table are calculated from actual settings of flow meters on the exposure system during dosimetry runs. The cigarettes used covered a fairly wide range of delivery of total particulate material. Plain and filter types were used, and cigarettes were made from two basic tobacco blends.

Animals were allocated to the various experimental groups and, for all except one group, were subjected to a smoke acclimatisation period prior to an exposure to smoke from cigarettes spiked with the particulate phase marker.

During acclimatisation, the duration of exposure was increased gradually over 5 days until animals were subjected twice daily to the exposure regime detailed in Table I for each cigarette type. This full exposure schedule was given on successive days and on the 3rd day an exposure to smoke containing the particulate marker was carried out.

Assessment of total particulate material deposition in animals was carried out using techniques based on the use of DCBP as a particulate phase marker [2]. Cigarettes were injected with DCBP (approx. 2.2 mg/cigarette) and suitably conditioned before being used. For all cigarettes, the transfer of the particulate phase marker to mainstream smoke and DCBP/TPM ratios were determined. Following exposure to "spiked" cigarettes, animals were rapidly killed and tissues removed for analysis of DCBP, and hence TPM, retained in the various regions of the respiratory system.

The respiratory system was divided into 5 regions: (*1*) skinned head (less

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TABLE I

CIGARETTE TYPES AND EXPOSURE CONDITIONS USED FOR DOSIMETRY STUDIES ON RATS

Cigarette	Description	TPM delivery to exposure chamber (mg/cig.)	CO delivery (mg/cig.)	Smoke dilution used (smoke/air v/v)	Chamber smoke concentration (mg/l)	Exposure [a] time (min)
A	70 mm, plain, flue-cured, all lamina	37.6	19.9	1 in 14.0	7.7	10
B	85 mm (with 15 mm tip) flue-cured Virginia blend	20.2	14.9	1 in 11.4	5.6	9
C	85 mm (with 21 mm tip) U.S. blend	22.6	17.2	1 in 5.4 1 in 9.8 1 in 28.5	13.4 7.3 2.5	9
D	85 mm (with 21 mm tip) Modified U.S. blend	18.7	15.3	1 in 9.8	6.8	8

[a] Equals nearest whole puff number to standard butt length of 23 mm.

brain), (2) skinned lower jaw and tongue, (3) larynx, (4) trachea and (5) main bronchi and lungs. Samples were placed in pre-weighed jars and stored under deep-freeze conditions pending analysis.

Tissue samples were cut into small sections and extracted for 3 hours with refluxing cyclohexane in Soxhlet thimbles containing sodium sulphate. The crude extracts were concentrated on a Büchi evaporator then applied to individual columns of alumina (Activity grade super 1). The columns were developed with cyclohexane which was discarded and the DCBP-containing fraction was eluted with ether in cyclohexane (15% v/v).

The eluate was concentrated to small volume under vacuum, made up to a standard volume (5, 10 or 25 ml) with added DDD as internal standard. Aliquots (1 μl) of these solutions were analysed for DCBP using a Perkin-Elmer Model F17 GLC fitted with dual Ni^{63} ECD at 300°C. The glass column (2 m × 3.0 mm i.d.) packed with 3.8% OV-1 on 80-100 mesh Chromosorb W (HP), was maintained at 260°C.

The DCBP was determined by a comparison with a calibration curve prepared from a series of standard solutions.

COHb levels in blood samples taken immediately following exposure were determined using an IL CO-Oximeter (Instrumentation Laboratories Limited).

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Animals subjected to smoke from cigarette A, were not acclimatised before exposure to DCBP-tagged smoke was carried out.

The effect of varying smoke dilution on TPM deposition and pattern of distribution of TPM in the respiratory system was carried out using cigarette C.

RESULTS

Raw data derived from animals exposed to smoke from each of the cigarettes used for this work are shown in Table II where deposition in the head and lower jaw samples has been combined to give total head deposition. Conditions varied to some extent for each of the series of exposures and detailed comparison of the data in this form is not particularly useful. However, the results do raise several interesting points which are worth commenting upon at this stage.

COHb levels were very similar in all groups of animals with mean values ranging from 25.7% to 33.0% COHb. Animals clearly did inhale smoke vapour phase and DCBP determinations confirmed that smoke particulate material was deposited in all parts of the respiratory system. Without exception, TPM load was greater in the lungs than in any other part of the respiratory system of the animals. Compared with the level of particulate deposition in the complete lower respiratory system, the mass of TPM deposited in the head of exposed rats was modest. Under the exposure conditions used for this part of the work, TPM deposition levels were within the approximate range of 350 μg—850 μg/animal. TPM retention per animal for the tissues examined was calculated at from 0.18% to 0.37% of the mainstream TPM which passed through the exposure chamber.

The calculation of percentage distribution of TPM detected in the various tissue samples analysed is shown in Table III. For all animals examined in this series, the largest proportion of TPM was found in the lower respiratory system. A mean of 17.9% of total TPM was detected in the head of one group of rats. For the remaining three groups, taking combined data for male and female animals, less than 10% of TPM was recovered from the complete head. The distribution of TPM marker in the head of these rats was low, when comparison is made with figures obtained for other laboratory rodents [3].

The animals exposed to smoke from cigarette A showed the highest per cent deposition of particulates in the head. Rats in this group were exposed without prior acclimatisation to smoke from high delivery, untipped cigarettes at the highest chamber smoke concentration used in this part of the study. Later (Table V), it is shown that low deposition of TPM in the head occurred in rats exposed to an even higher smoke concentration than that to which cigarette A animals were subjected. Whether the process of acclimatisation to smoke or filtration of mainstream smoke affects the deposition pattern in rats is not yet known. There was no obvious effect on deposition pattern due to exposure to smoke from distinctly different types of tobacco.

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TABLE II

DEPOSITION OF TPM IN RATS EXPOSED TO SMOKE FROM FOUR DIFFERENT CIGARETTES

Figures shown are mean and (S.D.).

Cigarette	Smoke dilution	Number and sex of animals	Mean body weight (g)	Mean TPM deposited (with S.D.)				Total respiratory [a] system TPM (μg)	Mean blood COHb (%)
				Head (μg)	Larynx (μg)	Trachea (μg)	Lungs (μg)		
A	1 in 14.0	6 Male	214	147.6 (37.6)	47.9 (48.8)	34.8 (19.5)	596.1 (254.2)	826.3 (254.3)	26.5 (8.1)
B	1 in 11.4	9 Female	197	64.2 (34.3)	31.0 (27.6)	21.3 (12.2)	647.3 (195.8)	763.8 (226.4)	26.1 (6.5)
C	1 in 9.8	6 Female	192	36.5 (20.2)	7.9 (3.9)	6.7 (5.4)	540.0 (203.2)	591.1 (202.3)	32.7 (6.8)
C		6 Male	216	43.4 (20.9)	10.6 (4.8)	5.4 (11.5)	618.8 (193.8)	678.2 (197.0)	33.0 (6.2)
C Pooled data	1 in 9.8	12	204	40.0 (20.8)	9.3 (4.6)	6.0 (4.0)	579.4 (202.4)	634.7 (204.4)	32.9 (6.5)
D	1 in 9.8	6 Female	186	35.0 (17.3)	5.3 (2.0)	7.3 (3.8)	318.7 (193.5)	366.3 (207.0)	26.8 (6.3)
D		6 Male	225	16.4 (7.9)	7.7 (6.1)	7.6 (4.3)	393.6 (122.1)	425.3 (133.8)	25.7 (5.7)
D Pooled data	1 in 9.8	12	206	25.7 (16.3)	6.5 (4.7)	7.5 (4.1)	356.2 (166.1)	395.9 (176.8)	26.3 (6.1)

[a] Head, larynx, trachea and lungs.

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TABLE III

MEAN PERCENTAGE DISTRIBUTION OF TPM IN WHOLE RESPIRATORY TRACT OF RATS EXPOSED TO SMOKE FROM FOUR DIFFERENT CIGARETTES

Cigarette	Smoke dilution	Number and sex of animals	Mean body weight (g)	Percentage distribution of TPM			
				Head (%)	Larynx (%)	Trachea (%)	Lungs (%)
A	1 in 14.0	6 Male	214	17.9	5.8	4.2	72.1
B	1 in 11.4	9 Female	197	8.4	4.1	2.8	84.7
C	1 in 9.8	6 Female	192	6.1	1.9	1.1	90.9
		6 Male	216	6.4	1.5	0.9	91.2
Pooled data	1 in 9.8	12	204	6.3	1.7	1.0	91.1
D	1 in 9.8	6 Female	186	9.6	1.5	2.0	87.0
		6 Male	225	3.9	1.8	1.8	92.6
D Pooled data	1 in 9.8	12	206	6.8	1.7	1.9	89.8

TPM was detected in substantial amounts in the lungs of animals. It follows that TPM dose for the various regions, expressed as μg TPM/g of tissue (Table IV), should be heaviest in the lungs and relatively low in the other regions of the lower respiratory system. There was no evidence, using this method of expressing dose, of particularly high deposition of TPM in either the larynx or trachea of rats.

Where direct comparisons could be made (cigarettes C and D) statistical analysis did not show any significant differences between sexes in either mass TPM deposition or TPM dose/g tissue (Table IV) to any region of the respiratory system.

To assess the effects of differences in smoke concentration on deposition characteristics, pre-acclimatised animals were subjected to smoke from cigarette C over a wide range of concentrations. Chamber concentrations of smoke at the dilutions used are shown for each group of animals, together with appropriate dosimetry data, in Table V.

As smoke concentrations in the exposure chamber increased, TPM mass deposited in the animals and blood COHb levels increased. Despite the changes in mass TPM deposition, the overall deposition pattern remained the same. The largest proportion of TPM reached the lower respiratory

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TABLE IV

DEPOSITION OF TPM PER UNIT WEIGHT OF TISSUE IN RATS EXPOSED TO SMOKE FROM FOUR DIFFERENT CIGARETTES

Figures shown are mean and (S.D.)

Cigarette	Smoke dilution	Number and sex of animals	Mean body weight (g)	Larynx (μg/g)	Trachea (μg/g)	Lungs (μg/g)	Complete lower respiratory system (μg/g)
A	1 in 14.0	6 Male	214	442.9 (360.0)	310.6 (119.0)	549.2 (290.7)	515.2 (250.2)
B	1 in 11.4	9 Female	197	447.7 (389.5)	399.6 (272.8)	601.9 (189.1)	583.4 (185.6)
C	1 in 9.8	6 Female	192	102.6 (33.4)	99.8 (67.8)	464.7 (170.4)	424.4 (155.1)
		6 Male	216	133.0 (57.7)	84.3 (27.5)	521.9 (159.5)	475.7 (143.8)
C Pooled data	1 in 9.8	12	204	117.8 (49.5)	92.1 (52.3)	493.3 (167.8)	450.1 (151.7)
D	1 in 9.8	6 Female	186	75.1 (26.6)	136.8 (61.1)	294.0 (175.4)	274.1 (161.6)
		6 Male	225	106.8 (90.1)	125.7 (76.9)	334.9 (121.3)	311.2 (114.4)
D Pooled data	1 in 9.8	12	206	90.7 (68.4)	131.3 (69.7)	314.5 (152.1)	292.7 (139.3)

region, particularly the lungs, and only a relatively small proportion deposited in the head. Statistical analysis revealed no significant differences in percentage deposition level at the three smoke concentration levels, although percentage deposition in the lungs did tend to fall and in the head to increase slightly as the concentration of smoke increased in the exposure chamber.

It is interesting to relate TPM deposition in the various respiratory regions to smoke concentration levels experienced by the three groups of rats exposed to smoke from cigarette C. In Table VI, the values for mean TPM dose to each of the various respiratory regions are expressed as ratios related to the corresponding TPM level found after exposure at the lowest smoke concentration. Similarly, smoke concentrations are expressed as ratios relative to lowest concentration i.e. at the dilution level 1 in 28.5, smoke : air.

The ratios of total deposition of TPM in rats, and of deposition of TPM in the lower respiratory system, lungs and larynx were very similar though slightly lower than the smoke concentration ratios for the different smoke dilutions. The trachea and head deposition ratios did not match smoke concentration ratios quite so closely.

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TABLE V

DEPOSITION OF TPM IN MALE RATS EXPOSED TO SMOKE FROM CIGARETTE "C" AT DIFFERENT CONCENTRATIONS

Figures shown are group mass mean deposition (S.D.) and mean % deposition

Chamber TPM concentration (mg/l)	Number of animals	Mean body weight (g)	TPM deposited						Mean blood COHb (%)
			Head (μg) (%)	Larynx (μg) (%)	Trachea (μg) (%)	Lungs (μg) (%)	Lower [a] respiratory system (μg)	Total respiratory system TPM (μg)	
2.5	6	223	11.5 (2.9) 4.6	4.2 (2.7) 1.7	2.4 (1.2) 1.0	233.5 (102.4) 92.8	240.1	251.6 (100.7)	19.0 (1.6)
7.3	6	216	43.4 (20.9) 6.4	10.6 (4.8) 1.5	5.4 (1.5) 0.9	618.8 (193.8) 91.2	634.8	678.2 (197.0)	33.0 (6.2)
13.4	4	223	94.2 (50.0) 8.4	19.8 (9.6) 1.8	16.7 (12.8) 1.5	994.5 (287.5) 88.4	1031.0	1108.3 (311.8)	46.0 (8.1)

[a] Sum of means of larynx, trachea and lungs.

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

TABLE VI

THE RATIOS OF SMOKE CONCENTRATIONS AND MASS TPM DEPOSITED IN VARIOUS REGIONS OF THE RESPIRATORY SYSTEM OF RATS EXPOSED TO SMOKE FROM CIGARETTE "C" OVER A RANGE OF DILUTIONS

Dilution level (smoke/air v/v)	Smoke concentration ratio	Head	Larynx	Trachea	Lung	Lower respiratory system	Total TPM deposited
1 in 28.5	1	1	1	1	1	1	1
1 in 9.8	2.92	3.77	2.52	2.25	2.65	2.64	2.70
1 in 5.3	5.36	8.19	4.71	6.96	4.26	4.29	4.41

DISCUSSION

Analyses of respiratory system tissues confirmed that smoke particulate material effectively penetrated to the lungs of rats exposed on the new exposure system used for this work. Without exception, for a particular exposure situation TPM deposition was always highest in the lung, in comparison with the larynx, trachea and head of the rat.

Deposition in the head of rats in all groups, irrespective of cigarette type, restraining tube or smoke concentration used, was relatively low. The highest head deposition of TPM, expressed as a percentage of TPM in the complete respiratory system, was 17.9%. In other groups of animals TPM deposition in the head was consistently less than 10%. This finding is of interest in relation to other figures published in the literature for the rat and other rodent species [3], because it contradicts the view [4] that filtration of TPM in the nasal region of small laboratory animals is a major obstacle to the development of inhalation toxicity studies with cigarette smoke.

TPM deposition in the head was highest in those rats which had not been acclimatised before being exposed to smoke from "spiked" cigarettes. Acclimatised rats in other groups exposed at similar concentrations of smoke showed a much lower proportion of TPM in the head. Although no firm conclusions can be drawn from the comparison of data from the different groups, the contrast in deposition pattern is striking and the question of acclimatisation should be investigated more fully.

Information in this study relates to samples from 45 rats only. Analysis of a total of around 80 rats, including data not recorded in this paper, give a consistent picture of a low percentage TPM deposition in the head. The data shown here are based on analyses carried out following careful, prolonged and repeated extraction of samples. As far as is known they represent accurately the actual and relative amounts of TPM in the various parts of the respiratory system of the exposed animals. The evidence presented here seems to show that for the rat *in our exposure system*, at least, nasal filtration was not a major obstacle to effective dosing of the lower respiratory

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system with smoke particulate material. It is significant that rats exposed under the conditions used in these dosimetry studies do show within a relatively short time consistent and quite marked changes in lower respiratory system pathology. This important aspect of our work will be reported in detail as soon as possible.

The difficulty of comparing inhalation studies carried out in different laboratories, using different exposure systems, has been stressed before. Figures presented here can be taken as relevant only to the exposure system and conditions used for our work. They can not be used to draw conclusions about dosimetry characteristics of rats in general, or for animals exposed under a variety of conditions on different smoking machines.

This qualification is perhaps re-inforced by recent work [5] on the Syrian golden hamster. In animals exposed in one system ("closed") TPM deposition in the head was 26.3% of total respiratory system load. For animals exposed in a second system (Hamburg II) the head deposition was almost halved, at 14.7% of a reduced total respiratory system load. Whatever the reason for the shift in deposition pattern, this experiment illustrates clearly that TPM mass deposition and distribution pattern may be affected by the exposure system used.

For the range of smoke dilutions reported here, TPM load to the lower respiratory system of animals ranged from a mean of 0.29 mg to 1.03 mg TPM per animal. A lung TPM dose of approx. 1 mg was associated with a high mean COHb level of 46.0%. In our system, for a regime of 2 exposures per day separated by an interval of 4 h, the upper value of approx. 1 mg TPM per session, appears to be close to the maximum TPM dose which animals will tolerate reasonably well following a short acclimatisation period. Whether this dose level could be increased substantially with a more prolonged acclimatisation of animals has not yet been determined.

Over the range of smoke dilutions which can probably be most usefully used for long-term inhalation toxicity studies (1 in 5 to 1 in 30 smoke : air, v/v) mass TPM deposition in the respiratory system, but not the distribution pattern, was affected by the chamber smoke concentration. TPM deposition increased as chamber concentrations increased, even at the highest concentrations used, when smoke was obviously markedly irritant to the rats. In the small experiment reported here, the increase in the ratio of TPM load to the various respiratory tissues tended to be less than the increase in ratio from lowest to higher smoke concentrations. More work is needed to clarify the effect of duration of exposure and smoke concentration on the actual dose of TPM retained by animals.

Mean levels of TPM retained in rats did follow smoke concentration gradient quite closely. However, it is apparent from calculated variance of means for all groups of rats, that the range of deposition of TPM in animals exposed under the same conditions was quite wide. For the lungs a two- to four-fold difference in TPM load between the highest and lowest dose was common in a group of, say, 6 rats. Similar variability in dose within groups of animals exposed under the same conditions has been shown for other species [3].

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ACKNOWLEDGEMENT

We are pleased to acknowledge the excellent technical assistance given by Mr. B.J. Dyas.

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small experiment reported here, the increase in the ratio of TPM load to the

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APPENDIX XI

A. Budgetary Summary

B. Budgetary Projections

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HARVARD UNIVERSITY

OFFICE FOR RESEARCH CONTRACTS

AREA CODE 617 495-5501

HOLYOKE CENTER 458
1350 MASSACHUSETTS AVENUE
CAMBRIDGE, MASSACHUSETTS 02138

October 31, 1977

Account Number: 60-097-9006

Grant No.: Tobacco Companies

STATEMENT OF EXPENDITURES

September 1, 1976 to August 31, 1977

Salaries		$ 281,507.55
Fringe Benefits		$ 20,359.59
		$ 301,867.14
Supplies		$ 52,958.59
Tel & Tel		$ 61.23
Postage, Express & Freight		$ 900.18
Subscription Books		$ 2,913.02
Miscellaneous		$ 11,931.08
Rental of Equipment		$ 33,705.44
Services Purchased		$ 55,883.45
Xerox		$ 433.63
Travel		$ 21,972.99
Equipment		$ 6,456.75
Computer Services		$ ---0--
Use of Hospital Facilities		$ 2,487.28
TOTAL		$ 491,570.78

CUMULATIVE TOTAL: 9/1/72 - 8/31/77: $ 2,958,107.66

Total Money Received: $ 2,791,887.00

BALANCE: DEFICIT-------- $ (166,220.66)

PRESIDENT AND FELLOWS OF HARVARD COLLEGE

By: Anne Feehan Title: Contract & Grant Supervisor

Anne Feehan

100335757

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BUDGET

DIRECT COSTS ONLY

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel	369,714	399,290	430,597
Equipment	24,800	2,000	2,000
Supplies	65,100	69,350	73,785
Travel	11,100	11,500	11,900
Alterations	4,300	-------	-------
Charlesgate	50,000	55,000	60,000
Clinical Services	50,000	55,000	60,000
Other	47,000	52,010	53,847
Total	622,014	644,150	692,129

THREE YEAR TOTAL $1,958,2

10035357758

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

SUMMARY BUDGET BY UNITS

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Administration	74,205	76,621	81,310
Analytic Chemistry	69,648	68,478	73,816
Animal Inhalation	97,946	105,834	113,800
Bacteriology	81,365	87,074	93,024
Biochemistry	88,610	78,373	84,870
Biostatistics	39,930	41,856	44,461
Biostructure	70,310	75,914	80,848
Charlesgate	50,000	55,000	60,000
Clinical Services	50,000	55,000	60,000
	622,014	644,150	692,129

THREE YEAR TOTAL $1,958,2

10035357S9

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ADMINISTRATION

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

		First Year	Second Year	Third Year
Personnel		42,705	46,121	49,810
Equipment		1,500	------	------
Supplies		3,500	3,500	4,000
Travel	Domestic	3,000	3,000	3,000
	Foreign	2,000	2,000	2,000
Other		21,500	22,000	22,500
Total		74,205	76,621	81,310

THREE YEAR TOTAL $230,636

1003535760

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

CLINICAL SERVICES SUPPORT

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel			
Faculty	37,000	40,000	43,000
Fellowships	13,000	15,000	17,000
Total	50,000	55,000	60,000

THREE YEAR TOTAL $165,000

10035761

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

SATELLITE LABORATORY FACILITIES

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Charlesgate Building			
Rent	29,700	30,600	31,500
Utilities	12,000	12,500	13,000
Basic Maintenance and service contract	8,300	11,900	15,500
Total	50,000	55,000	60,000

THREE YEAR TOTAL $165,000

10035357G2

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOSTRUCTURE

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (Paul Davies)	100	$25,000	$5,250	$30,250
Technician	100	9,000	1,530	10,530
Technician	100	9,000	1,530	10,530
Supplies				
Chemicals, glassware, film, fixation materials				15,000
Travel				1,000
Other Expenses				
Medical illustration, journals, photogopying, maintenance service contracts				3,000
			TOTAL DIRECT COST	$70,310

10035357763

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOSTRUCTURE

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel	51,310	55,414	59,848
Supplies	15,000	16,000	16,000
Travel Domestic	1,000	1,000	1,000
Other	3,000	3,500	4,000
Total	70,310	75,914	80,848

THREE YEAR TOTAL $227,072

10035357C4

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOSTATISTICS

DETAILED BUDGET FOR FIRST 12-MONTH-PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (Clinton Sornberger)	100	$23,000	$4,830	$27,830
Equipment				
Hewlett-Packard 25 calculator (2)				400
Supplies				
Miscellaneous expendables				400
Travel				800
Other Expenses				
PROPHET (NIH) Computer costs				6,000
Harvard computing service				1,000
Computer hardware service contracts				2,500
Medical illustration (etc.) journals				1,000
			TOTAL DIRECT COST	$39,930

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOSTATISTICS

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

		First Year	Second Year	Third Year
Personnel		27,830	30,056	32,461
Equipment		400	------	------
Supplies		400	------	------
Travel	Domestic	800	800	1,000
Other		10,500	11,000	11,000
Total		39,930	41,856	44,461

THREE YEAR TOTAL $126,247

10035766

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOCHEMISTRY

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (David Drath)	100	$28,000	$5,860	$33,860
Research Assistant	100	12,000	2,040	14,040
Research Assistant	100	9,000	1,260	10,260

Equipment	
Gilford model 250 spectrophotometer	12,000
Quartz cuvettes	250
Yellow springs instrument oxygen monitor	1,700
Shandon Southern Power Supply	500
Supplies	
Experimental animals	4,000
Laboratory supplies	4,500
Travel	
Domestic	1,100
Foreign	900
Alterations	
Hood installation	2,800
Other Expenses	
Medical illustrations, publication costs, photography, photocopying, journals and books, professional societies	2,700
TOTAL DIRECT COST	$88,610

1003535767

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BIOCHEMISTRY

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

		First Year	Second Year	Third Year
Personnel		58,160	62,813	67,838
Equipment		14,450	------	------
Supplies		8,500	9,350	10,285
Travel	Domestic	1,100	1,200	1,400
	Foreign	900	1,000	1,000
Alterations		2,800	------	------
Other		2,700	4,010	4,347
Total		88,610	78,373	84,870

THREE YEAR TOTAL $251,853

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BACTERIOLOGY

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (Vijay Mahajan)	100	$26,000	$5,460	$31,460
Research Associate	100	14,500	2,465	16,965
Research Associate	100	9,000	1,440	10,440
Supplies				
Animals				8,000
Expendable supplies				9,500
Travel				800
Other Expenses				
Photocopying, illustration				2,400
Equipment maintenance and repair				1,800
			TOTAL DIRECT COST	$81,365

100353576

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

BACTERIOLOGY

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel	58,865	63,574	68,024
Supplies	17,500	18,000	19,000
Travel	800	1,000	1,000
Other	4,200	4,500	5,000
Total	81,365	87,074	93,024

THREE YEAR TOTAL $261,463

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ANIMAL INHALATION FACILITIES

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (Val Pochay)	100	$17,000	$2,890	$19,890
Machine Operators (2)	100	13,520	2,298	15,818
Animal Handlers (3)	100	22,740	3,638	26,378
Part-time crew	100	11,000	1,760	12,760
Equipment				
Racks and exposure tubes				2,000
Supplies				
Animals				4,500
Animal supplies				5,000
Cigarettes				5,000
Travel				500
Renovation				1,500
Other Expenses				
Machine maintenance				2,500
Medical illustration (etc.)				1,000
Service contract (air-conditioning)				1,100
			TOTAL DIRECT COST	$97,946

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Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ANIMAL INHALATION FACILITIES

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

	First Year	Second Year	Third Year
Personnel	74,846	80,834	87,300
Equipment	2,000	2,000	2,000
Supplies	14,500	16,500	18,000
Travel	500	500	500
Renovations	1,500	------	------
Other	4,600	6,000	6,000
Total	97,946	105,834	113,800

THREE YEAR TOTAL $317,580

10035357?2

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ANALYTICAL CHEMISTRY

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Principal Investigator (Melvin First)	VAR	$ 2,500	$ 388	$ 2,888
Co-Principal Investigator	80	18,000	2,790	20,790
Senior Research Associate	50	12,000	1,860	13,860
Research Associate	100	14,000	2,170	16,170
Shop (Mechanical & Electrical)	15	2,000	290	2,290

Equipment

Nitrogen determination apparatus for gas chromatography for nicotine analysis	2,500
Pyrolysis unit for gas chromatography	2,200
Temperature programmer for gas chromatography	1,300
Gas chromatography columns (4)	450

Supplies

Glassware, chemicals, microsyringes, maintenance and repair items for gas chromatography, mass spectrograph smoking machines, consumable office supplies	5,700

Travel 1,000

Other Expenses

Telephone, journals and publication costs, medical illustrations	500

TOTAL DIRECT COST $69,648

1003535773

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ANALYTICAL CHEMISTRY

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED

7/1/77 - 6/30/80

		First Year	Second Year	Third Year
Personnel		55,998	60,478	65,316
Equipment		6,450	------	------
Supplies		5,700	6,000	6,500
Travel	Domestic	1,000	1,000	1,000
Other		500	1,000	1,000
Total		69,648	68,478	73,816

THREE YEAR TOTAL $211,942

10035357274

Source: https://www.industrydocuments.ucsf.edu/docs/fjyl0000

ADMINISTRATION

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

7/1/77 - 6/30/78

Personnel	% Time	Salary	Fringe Benefits	Total
Administrative Assistant	100	$17,000	$2,890	$19,890
Secretary	100	10,500	1,785	12,285
Secretary	100	9,000	1,530	10,530
Equipment				
Typewriter, calculator, dictaphone, and miscellaneous equipment replacement				1,500
Supplies				
Postage				2,000
Stationery				1,500
Travel				5,000
Other Expenses				
Books and journals				2,000
Luncheons, site visit				4,500
Services, photocopy, medical illustration				15,000
TOTAL DIRECT COST				$74,205

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Source: https://www.industrydocuments.ucsf.edu/docs/fyj10000